A. M. A.
ARCHIVES OF
OPHTHALMOLOGY

Continuing the Publication
FOUNDED BY HERMAN KNAPP, 1869

EDITORIAL BOARD

FRANCIS HEED ADLER, Chief Editor
343 South Seventeenth Street, Philadelphia 3

WILLIAM ZENTMAYER, Philadelphia
W. L. BENEDICT, Rochester, Minn.
KENNETH C. SWAN, Portland, Ore.
WILLIAM F. HUGHES Jr., Chicago
DAVID G. COGAN, Boston
JONAS S. FRIEDENWALD, Baltimore
JOHN H. DUNNINGTON, New York

ASSOCIATES:

Alson E. Braley
F. Phinizy Calhoun Jr.
A. Gerard DeVoe
Trygve Gundersen
Joseph S. Haas
John E. Harris
John M. McLean
Paul W. Miles
Frank Payne
Ludwig von Sallmann
Henry P. Wagener
Maynard C. Wheeler

MAY 1954

VOLUME 51 NUMBER 5

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

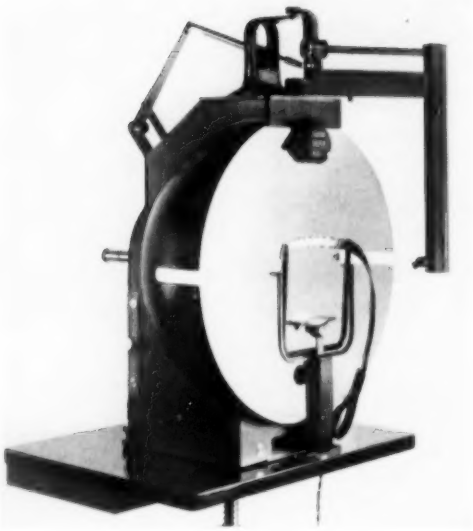
Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

TABLE OF CONTENTS FIRST PAGE

DOCTOR—

CHECK THE ADVANTAGES OF THESE TWO

Projection Perimeters



Goldmann Projection Perimeter
—Haag-Streit

Uniform illumination and variable at will. Complete independence of illumination of perimeter bowl from light outside as well as controlled constancy of contrast between basic illumination and brightness of object are some of the advantages. Targets of various sizes and colors and always exactly the same reproducible contrast are projected on field of perimeter. Movement of the targets is controlled by means of a handle which can be moved in any direction over a perimeter record chart. Position of handle on chart corresponds to position of target in hemisphere.

Aimark Projection Perimeter
—Curry & Paxton

The test stimulus is of uniform brightness and is made to travel centrally along the arc up to 100° on either side of central fixation object. Sixty-four different test stimuli may be presented by combinations of three control wheels on top of lamp housing. Apertures in wheel are all clear but of different sizes. Apertures in second wheel change colors from white to red, green or blue. Third wheel contains one free aperture and 3 free neutral filters of different optical densities. By means of a silently operated spring-loaded lever the stimulus in any part of an arc may instantaneously be extinguished or revealed by a flicker device. Recording is automatic.

If you do not have our instrument handbook with complete description of all equipment we handle—please write.

The House of Vision Inc.

30 NORTH MICHIGAN AVENUE, CHICAGO

MILWAUKEE • MINNEAPOLIS • DES MOINES

TABLE OF CONTENTS

ORIGINAL ARTICLES

Pathological Study of Retinoblastoma Treated by Radon Seeds and Radium Disks PAGE
H. B. Stallard, B.Chir., M.B., London, England 573

Biochemistry of the Eye

I. Chromatographic Investigation of Free Amino Acid Constituents of Vitreous Humor
John F. Wootton, M.S.; Roger G. Young, Ph.D., and Harold H. Williams, Ph.D., Ithaca, N. Y. ... 589

II. Gelatinous Protein of Vitreous Body
Roger G. Young, Ph.D., and Harold H. Williams, Ph.D., Ithaca, N. Y. 593

III. Lipids of the Lens, Cornea, Iris, Ciliary Body, and Retina
Barbara S. D'Asaro, M.N.S.; Roger G. Young, Ph.D., and Harold H. Williams, Ph.D., Ithaca, N. Y. 596

Glycolytic Activity of Ciliary Processes
Andrew de Roetth Jr., M.D., with the Technical Assistance of Mildred Orchen, B.A., New York .. 599

A Modified Krönlein Operation
Raynold N. Berke, M.D., Hackensack, N. J. 609

Use of Radioactive Phosphorus in Detection of Intraocular Neoplasms
I. J. Eisenberg, M.D.; I. H. Leopold, M.D., and D. Sklaroff, M.D., Philadelphia 633

Effect of Cigarette Smoking on Flicker Fusion Threshold
Lawrence L. Garner, M.D.; E. Franklin Carl, M.D., and Erwin E. Grossman, M.D., Milwaukee .. 642

Malignant Melanoma of the Iris and Ciliary Body of a One-Eyed Patient
Ivan J. Koenig, M.D., Buffalo 656

Benoxinate (Dorsacaine) for Rapid Corneal Anesthesia
Henry E. Schlegel Jr., M.D., and Kenneth C. Swan, M.D., Portland, Ore. 663

Outflow of Aqueous Humor
J. Stepanik, M.D., Vienna, and Lieutenant (jg) R. A. Kemper (MC), U.S.N.R. 671

Fibrin Film Treatment of Corneal Diseases
C. W. Weisser, M.D., Pittsburgh 681

Phasic Variations in Tonography
Harry Horwich, M.D., and Goodwin M. Breinin, M.D., New York 687

Clinical Evaluation of the Rodenstock Refractometer
R. Tully Bradford, M.D., Cincinnati, and Lawrence J. Lawson Jr., M.D., Chicago 695

CLINICAL NOTES, NEW INSTRUMENTS AND TECHNIQUES

Sterile Air in Intraocular Surgery
Paul C. Craig, M.D., Reading, Pa. 701

REGISTRY OF INTERESTING CASES

Iritis and Glaucoma Associated with Mumps
Ralph S. Riffenburgh, M.D., Pasadena, Calif. 702

ANNUAL REVIEWS

Diseases of the Retina and Optic Nerve
Henry P. Wagener, M.D., Rochester, Minn. 703

CORRESPONDENCE

Beryllium and Delayed Corneal Healing
A. Benedict Rizzuti, M.D., Brooklyn 725

Ocular Dominance and Handedness
John J. Stern, M.D., Utica, N. Y. 725
George E. Berner, M.D., Philadelphia 726

REGULAR DEPARTMENTS

News and Comment 728

Books 733

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $20.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Price, $10.00. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10.

A. M. A. Archives of Dermatology and Syphilology. Price, $12.00. Paul A. O'Leary, M.D., Chief Editor, 102 Second Ave. S.W., Rochester, Minn.

A. M. A. Archives of Ophthalmology. Price, $12.00. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5.

A. M. A. American Journal of Diseases of Children. Price, $12.00. Clifford G. Grulee, M.D., Chief Editor, 610 Church St., Evanston, Ill.

A. M. A. Archives of Pathology. Price, $8.00. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37.

A. M. A. Archives of Neurology and Psychiatry. Price, $12.00. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif.

A. M. A. Archives of Otolaryngology. Price, $12.00. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3.

A. M. A. Archives of Surgery. Price, $14.00. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10.

A. M. A. Archives of Industrial Hygiene and Occupational Medicine. Price, $8.00. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15.

Prices slightly higher in Canada and Foreign countries. Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript and the first carbon of an article should be provided, and must be double or triple spaced on one side of a standard size page, with at least 1-inch margin at each edge. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

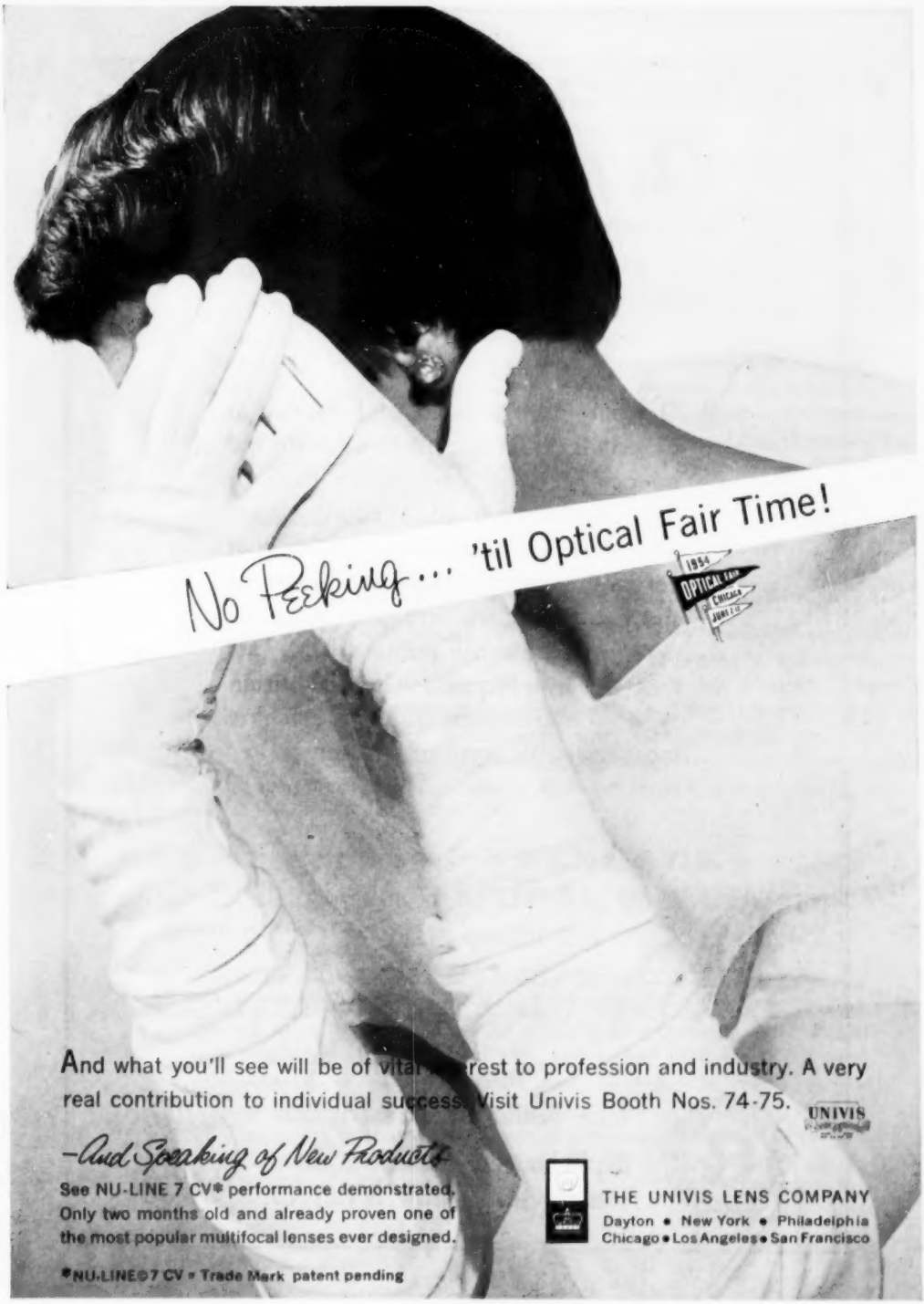
The maximum illustration space on a journal page is 5 by 8 inches. Original line drawings should not exceed 8½ by 11 inches. Oversized originals should be photographed and a print submitted within the 5 by 8 limits. Prints larger than 5 by 8 inches will be reduced in scale and/or cropped. Photomicrographs larger than 5 by 8 inches will be reduced in scale unless portions to be cropped are indicated by the author. Any cut-off marks should be made on the margins or mountings rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the authors name, an abbreviated title of the article, and top plainly indicated. Photographs should not be rolled unless too large to be sent flat. If mailed flat, protect them with several layers of corrugated board. A rolled photograph should face outward. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the *Quarterly Cumulative Index Medicus*, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the *Quarterly Cumulative Index Medicus*. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation, preferably that used in the *Quarterly Cumulative Index Medicus* subject entries, or all in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**


No Peeking... 'til Optical Fair Time!
1954
OPTICAL FAIR
CHICAGO
JUNE 7-9
And what you'll see will be of vital interest to profession and industry. A very real contribution to individual success. Visit Univis Booth Nos. 74-75.
UNIVIS
–And Speaking of New Products
See NU-LINE 7 CV* performance demonstrated. Only two months old and already proven one of the most popular multifocal lenses ever designed.
*NU-LINE©7 CV = Trade Mark patent pending
THE UNIVIS LENS COMPANY
Dayton • New York • Philadelphia
Chicago • Los Angeles • San Francisco

The Purpose of the Guild

- The aim of the Guild of Prescription Opticians of America is to advance the science of ophthalmic optics through the development of a country-wide ethical optical dispensing service that comprehensively meets the needs of the Eye Physicians and their patients; and to educate the public to the fact that the Eye Physician-Guild Optician type of eye service truly renders the most desirable form of eye care.

This statement of the Guild's purpose is reprinted from the cover of the REFERENCE LIST OF GUILD OPTICIANS, a geographical index of all our members. If you would like a copy, just drop a two-penny post card to

The Guild of Prescription Opticians of America, Inc.
110 E. 23rd Street New York (10) N.Y.

Look what
Bausch & Lomb
has done with

Trifocals

a **NEW CONCEPT** of the trifocal lens

BASED ON the optical solution to the problems of diminishing accommodation To supplement the progressive loss of accommodation is, of course, the purpose of multifocal lenses. Correlation of the many studies of accommodative amplitude, plus original analyses of contemporary professional prescriptions, revealed a mathematically-precise formula for relating intermediate power of correction to near power. This work, done by the Bausch & Lomb Department of Ophthalmic Research and Development, has resulted in the design of the integrated series of functional trifocals, which provides, in every power, the proper near-intermediate ratio.

AND MADE POSSIBLE by Bausch & Lomb glass technology Production of trifocal lenses in a series of graduated intermediate powers requires special glass types of specific characteristics. Not only must glasses be available of specified refractive index—they must have desired color-dispersion values, and must be correct in properties of softening-point and thermal coefficient of expansion to provide for proper fusing. Development of all needed glass types with correct characteristics is the accomplishment of Bausch & Lomb glass technologists.

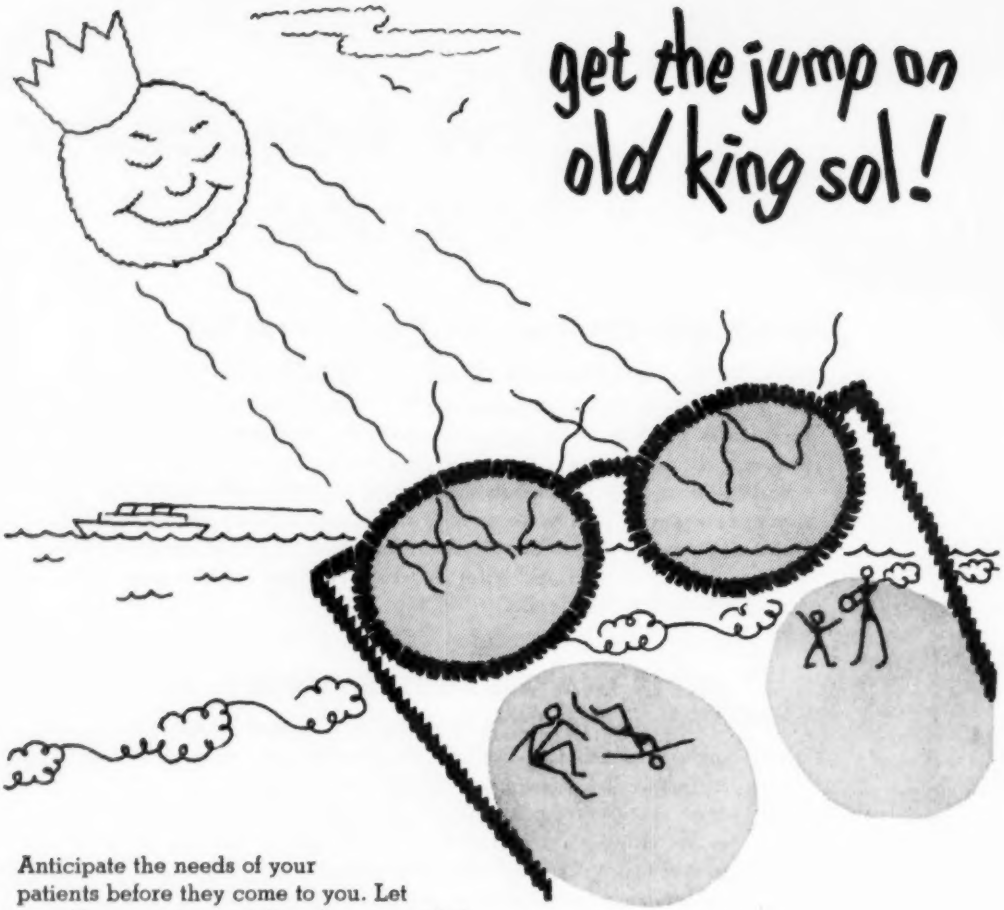
the integrated series* of **PANOPTIK** functional trifocals provides **NATURAL VISION** from infinity to near point because it provides correct intermediate power for every near point add Called for is a series of trifocals of the following intermediate-near ratios: for reading adds +1.50 and +1.75, intermediate power of 35%; for reading adds +2.00 to +2.75, intermediate power of 55%; for reading adds +3.00 and over, intermediate power of 66%. You can prescribe Bausch & Lomb Panoptik Trifocals (or the matching series of Straight-Tops) specifying only reading add power, with assurance that correct intermediate power will be provided for maximum visual comfort and efficiency—for natural vision at all distances for all near point adds. *In Soft-Lite, too.*

*Patent applied for

Exhibit Dates
June 5-10

BAUSCH & LOMB
SINCE 1853

get the jump on old king sol!



Anticipate the needs of your patients before they come to you. Let your Benson representative show you what we believe to be the widest selection of sun glasses in the field.

He'll be able to supply **G15** in bifocals and trifocals, and single vision in uniform density . . . **Bifocals and trifocals** of your choice in greens 2 and 3 in regular size as well as LARGE sun glass size . . . And, in addition, a full line of the popular **AO CALOBARS** and **B & L RAY-BANS** plus hundreds of beautifully laminated frames (plain or with precious metal trim) in plano and prescription form.

In case the Benson sales representative misses you, inquire at any Benson Laboratory about the complete line of Benson sun glasses.

Since 1913

Benson
OPTICAL COMPANY

Executive Offices • Minneapolis, Minn.

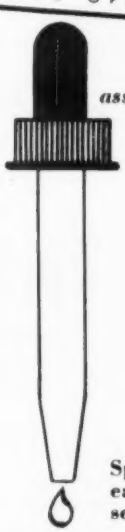
LABORATORIES IN LEADING UPPER MIDWEST CITIES

drop for drop...

and minim for minim...

ISO-SOL®

STERILE OPHTHALMIC SOLUTIONS



assure the utmost in:

- CLINICAL EFFECTIVENESS
- PATIENT PROTECTION

Scientifically prepared,
ISO-SOL ophthalmic solutions are:

- physiologically active
- exceptionally well tolerated
- buffered for stability
- sterile and bacteriostatic

and available in a variety of preparations routinely employed in ophthalmologic practice.

Specify ISO-SOL— each dropper bottle is sterile, sealed and dated.

Now Available...

Myotics, Mydriatics, Antiseptics and Lubricants.
Pilocarpine HCl. ½, 1, 2, and 4% in 15 cc. sterile, sealed dropper bottles.
Eserine Salicylate ⅛, ¼ and ½% in 7.5 cc. sterile, sealed dropper bottles.
Atropine Sulfate U.S.P. ½, 1, 2 and 4% in 4 cc. sterile, sealed and dated dropper bottles.
Homatropine Hydrobromide U.S.P. 2 and 5% in 4 cc. sterile, sealed and dated dropper bottles.
Note: ISO-SOL Eserine Salicylate solutions will not discolor.

Write for a descriptive list of all ISO-SOL products.

MYOTICS
MYDRIATICS
ANTISEPTICS
LUBRICANTS

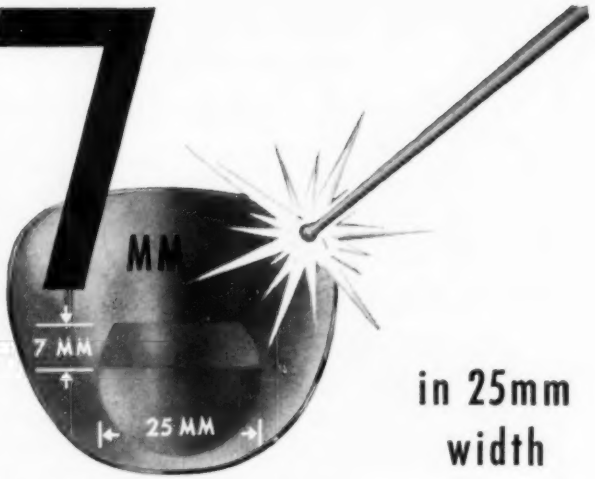
THE ISO-SOL® COMPANY, INC.

130 FLATBUSH AVENUE
BROOKLYN 17, N. Y.

pioneer specialists in sterile ophthalmic pharmaceuticals

IN CANADA: RANAH CO., 1245 ST. CATHERINE ST. W., MONTREAL

NEW! 7 MM



in 25mm width

Now a standard stocked design in

Titmus Straight Top Trifocals

A new star is born! It's the 7mm intermediate trifocal in a 25mm width, formerly a special factory order. The ever increasing popularity of this trifocal has made it a Titmus standard stocked lens . . . ready for immediate delivery!

For the average patient, the 25mm width is neither too large nor too small and provides a comfortable reading area. The 7mm intermediate allows a wide field of vision without encroaching too much on the distance portion of the lens. For these reasons, more and more lenses of this design are being prescribed daily.

As in all Titmus Trifocals, this style lens has the following quality features:

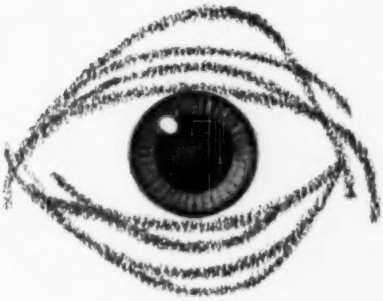
OPTICAL FINISH: Pitch polished.
OVERALL SIZE: 55mm sq. x 60mm diagonal.
BASE CURVES: +6.50, 7.50 and 8.50.
READING ADDITIONS: +1.00 through +3.00 in ¼ D.
INTERMEDIATE POWER: 50% of reading addition.
DECENTERED: 2 mm.
SEGMENTS: Barium glass for minimum color.
OPTICAL CENTER OF SEGMENT: 2mm down in reading.

In White and Velvet-Lite A & B.

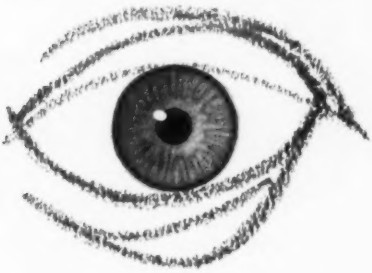
Titmus OPTICAL COMPANY, INC.
PETERSBURG, VIRGINIA

RAPID ACTION

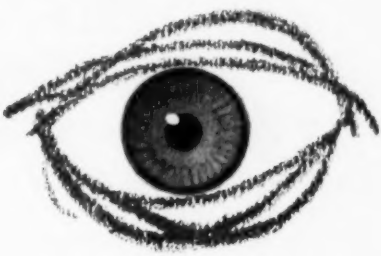
RAPID ACTION



RAPID RECOVERY



RAPID RECOVERY



A TIME SAVER IN CYCLOPLEGIA AND MYDRIASIS

A new, virtually non-irritating cycloplegic-mydriatic compound with marked advantages in rapidity of action (30-60 minutes), depth of depression of accommodation, and promptness of recovery ... 12-24 hours *without* a miotic ...

Now ... Council Accepted

CYCLOGYL®

Hydrochloride

brand of CYCLOPENTOLATE hydrochloride

Effective in cases of darkly pigmented eyes normally refractory to cycloplegics,[1] CYCLOGYL Hydrochloride does not appreciably affect intra-ocular pressure, and may be used with safety in all age groups. It "may successfully replace, or will certainly be a useful adjunct, to the use of homatropine and even atropine for routine office refraction."[2]

Write for literature

CYCLOGYL (Hydrochloride) Available in 0.5% and 1.0% Solution, in 15 cc. Bottles; 1.0% Solution, in 2 cc. Bottles

Schieffelin & Co., pharmaceutical and research laboratories since 1794

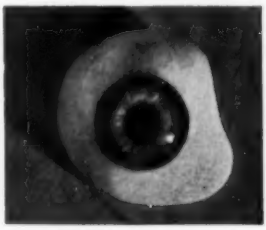
18 Cooper Square, New York 3, N. Y.

1. Gettes, B. C., and Leopold, I. H.: A. M. A. Arch. of Ophth. 49:24 (Jan.) 1953.
2. Stolzar, I. H.: Am. J. Ophth. 36:110 (Jan.) 1953.

Specialists in ALL TYPES of Plastic and Glass Artificial Human Eyes Exclusively

MADE TO ORDER IN OUR OWN LABORATORY

Doctors are invited to visit



REFERRED CASES CAREFULLY ATTENDED AND SATISFACTION GUARANTEED

EYES ALSO FITTED FROM STOCK

Plastic or Glass Selections Sent on Memorandum upon Request

Implants and Plastic Conformers in Stock

FRIED AND KOHLER, INC.

665 FIFTH AVENUE
near 53rd St.

NEW YORK, N. Y.
Tel. ELdorado 5-1970

THE "AMIC" MACULA DEFICIENCY TESTER

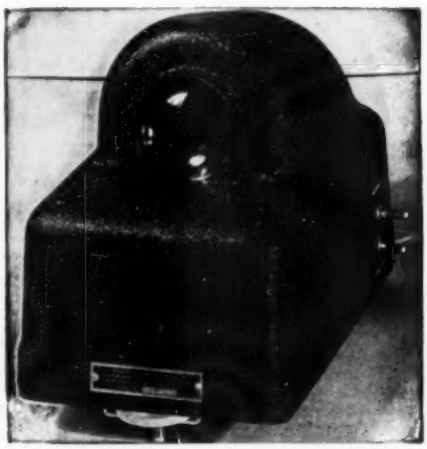
developed by Dr. M. Goldschmidt,
formerly Professor of Ophthalmology, Leipzig University

An instrument to detect early abnormalities of the macula lutea—in a short routine check-up.

As a new instrument of diagnosis, it should belong to the standard equipment of every ophthalmologist.

Write for further information

Recently made available for immediate delivery



AMERICAN MEASURING INSTRUMENTS CORPORATION

21-25 44th Ave., Long Island City 1, N. Y.

1954 OPTICAL FAIR

CHICAGO JUNE 2-12

Put the Fair on your Vacation Schedule

It's something you'll really enjoy
and you'll pick up a lot of information and ideas
from the many, many special features and exhibits.

Come see us at Booths 48-49 and 50.

The latch string is out.

Exhibit Days • June 5-10
Daily Guest Hours • 2:00 P. M. to 6:00 P. M.
Sunday Guest Hours • 10:00 A. M. to 6:00 P. M.

Continental
INDIANAPOLIS

transactions of the

AMERICAN OPHTHALMOLOGICAL SOCIETY

89th Annual Meeting, Hot Springs, Virginia, 1953

These twenty-one papers represent new findings and research in ophthalmology. Each paper presents in detail the experimental and clinical evidence on its subject, and is followed by a summary of the discussion that took place at the meeting. The volume also includes the minutes of the eighty-ninth annual meeting and theses of candidates accepted for associate membership in the American Ophthalmological Society. 775 pp., illus. April. $18.00.

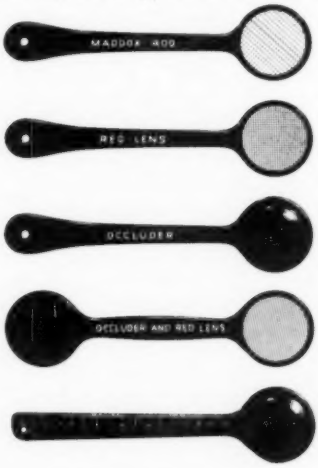
And remember the **CUMULATIVE INDEX (1933-1952)** of the American Ophthalmological Society for Volumes xxxi-l. It contains a complete index by author and subject of the various papers of the last twenty years. $2.00.

Available from

Columbia University Press • 2960 Broadway, N.Y. 27

PLASTIC OCCLUDERS

Available in black or white handles, 25 cm. long occluders are cupped to 70 mm. radis and Red Lens are plano.



Single End Handles are:
Occluder with plain handle.
Occluder with 160 mm. scale on handle.
Small red lens handle 12 cm. long.
Red lens handle 25 cm. long.
Red multiple maddox rod handle.

Double End Handles:
Red lens and Occluder.
Maddox rod and Occluder.
Maddox rod and Red Lens.
Double Maddox Rod.

Available at all surgical and Optical suppliers.

Manufactured by

4920 N. LAWRENCE ST. **R. O. GULDEN** PHILADELPHIA 20, PA.

Our complete brochure is now available.

THE NEW Rodenstock EYE-REFRACTOMETER

for fast, accurate diagnosis

Excellent for the objective determination of refractions of the human eye, the Rodenstock eye-refractometer permits instantaneous readings of spherical and cylindrical refractions including inclination of the axis.

It enables you to diagnose objectively problem cases like children, illiterates and cases of pin hole pupils, as size of pupil has no effect. Eliminates time consuming basic diagnosis so tiring to the patient. Particularly helpful in difficult cases of strong astigmatism and sensitive or nervous patients. This instrument tends to stimulate the patient's confidence in the doctor as well as self-confidence of the patient.

Range from plus 20. O D to minus 20. O D

This is truly an instrument of the future . . . available to you today!

Ask a doctor who owns a Rodenstock!

KRAHN UNIVERSAL REVOLVING STAGE for Ophthalmological Examinations

The modern ophthalmic unit with hydraulic height adjustment! Conveniently accommodates all or any instruments of any make, such as:

- Binocular Slit Lamp
- Eye-Refractometer
- Ophthalmometer
- Binocular Ophthalmoscope
- Phoropter
- Projector
- Trial lens set
- Orthoptic Instruments

SLIT LAMP BINOCULAR MICROSCOPE

Model HSE (Illustrated on Stage)

- One-hand control lever (joy-stick) for all direction positioning
- Combined adjustability for Slit Lamp and Microscope
- Same center level for slit and microscope at every axial rotation
- Hruby lens
- Brilliant, sharply defined slit
- Interchangeable to Binocular Ophthalmoscope

OPHTHALMOMETER (Illustrated on Stage)

- One-hand control lever (joy-stick) for all direction positioning
- Rapid and accurate measurements by new optical technique
- Optical readings of refractive values and radii
- Bright fixation point
- Tabo and International Schema
- Test images according to Javal
- Specially adapted for Contact Lenses

Range of Measurement:
Refractive power 30-60 diopters
Radii 5.5-11 mm

ANTON HEILMAN AO-554

75 Madison Avenue, New York 16, N. Y.

Send catalog on:

- ☐ Rodenstock Eye-Refractometer
- ☐ Rodenstock Vertex Refractionometer
- ☐ Rodenstock trial lens sets
- ☐ Universal Revolving Stage
- ☐ Krahn Slit Lamp Binocular Microscope (HSE)
- ☐ Krahn Ophthalmometer (BE)
- ☐ Krahn Binocular Ophthalmoscope (OFE)
- ☐ Krahn Prism Exophthalmometer
- ☐ Eye Surgical Instruments

Name .....

Address .....

City ..... State .....

THE "LACRILENS" ® IS A SAFE LENS

The Test Of Time Proves That The "LACRILENS"® Contact Lens Can Be Worn For Long Periods Of Time In Aphakia And In All Sports, Including Swimming.

WRITE FOR BROCHURE

Obrig Laboratories Inc.

49 EAST 51st STREET • NEW YORK, 22, N. Y.

Manufacturers of all types of Contact Lenses

BRANCHES IN

PHILADELPHIA MONTREAL JOHANNESBURG

Obrig ®

Do you dispense glasses?

We are one of the oldest, and most reputable wholesale opticians in the east, serving the discriminate ophthalmologist.

An inquiry from you will bring a representative at your convenience to outline our superior service plan.

MAX ZADEK, INC.

established 1904

115 Fulton Street New York 38, N. Y.

storz
Surgical Instruments

Fine Eye Forceps

Newly Developed Models

247c* Forceps, Levator, BERKE **$15.00**

249½* Corneo-Scleral Forceps, KIRBY: light **16.75**

266b* Forceps, Iris, CHANDLER **9.50**

273b* Forceps, Iris, Gill Handle, delicate **12.50**

300 * Forceps, Fixation, THORPE: for friable conjunctiva **14.75**

326b* Forceps, Corneal and Splinter, THORPE **8.75**

327a* Forceps, Suturing, CASTROVIEJO: teeth 0.9mm **11.50**

327b* Forceps, Suturing, CASTROVIEJO: teeth 1.5mm **11.50**

335d* Forceps, Suturing, LEAHEY: right angled teeth **17.50**

335e* Forceps, Suturing, LEAHEY: forward angled teeth **17.50**

389 * Forceps, Muscle, GUNDERSON **14.50**

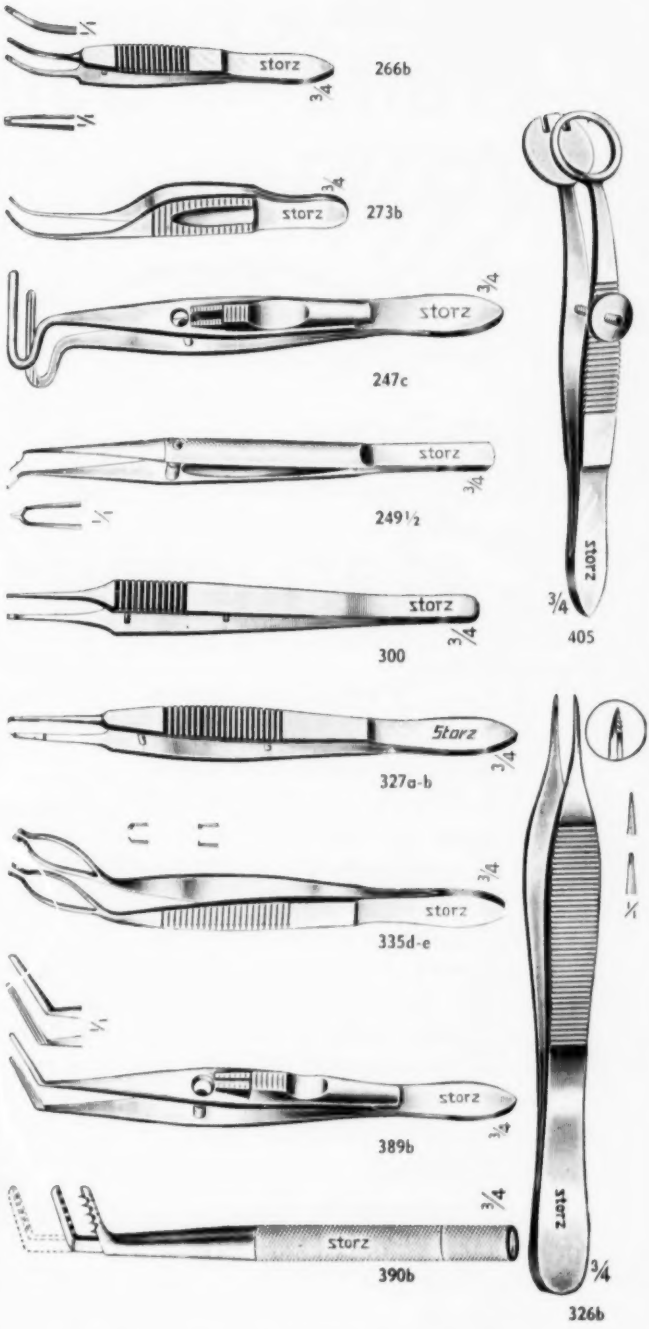
390b* Clamp, Muscle, BERENS **21.50**

405 * Forceps, Marginal Chalazion, LEAHEY **13.75**

* Stainless Steel

storz

Catalog sent upon request



Storz Instrument Company

4570 Audubon Ave. **St. Louis 10, Missouri**

available soon!

OPHTHALMOS

sterile, stable, eye medications in the new

steridroppa*

Single dose sterile eye solutions
in disposable dropper units, developed by
Robert R. Feinstein and Associates in collaboration with major eye hospitals in the U.S.A.
A major advance in the maintenance of sterility in operating procedure and post operative therapy. A necessity in every eye operating room and wherever eye injuries are treated.
STERIDROPPAS contain all important solutions required for ocular surgery.

* trade mark
pat. pend.

write now for further details to

OPHTHALMOS, INC.
4808 BERGENLINE AVE.
UNION CITY, N. J.

just pin this to your letterhead and mail

Please Send Details on
Ophthalmos
steridroppa
Solutions

A. M. A.
ARCHIVES OF OPHTHALMOLOGY

VOLUME 51 MAY 1954 NUMBER 5

COPYRIGHT, 1954, BY THE AMERICAN MEDICAL ASSOCIATION

PATHOLOGICAL STUDY OF RETINOBLASTOMA TREATED BY RADON SEEDS AND RADIUM DISKS

H. B. STALLARD, B.Chir., M.B.
LONDON, ENGLAND

FIRST, I thank you most sincerely for the great honor you have done me in inviting me to give this lecture in memory of the late Charles H. May. Charles H. May came to New York at the age of 4, and in this great city his work as a famous teacher, a skillful surgeon, and a man of absolute integrity of character and high ethical standards justifiably earned him an international reputation and the high regard of his colleagues in this and in many countries abroad. His well-known book, which ran to 18 editions during his life and is being continued by his nephew, Dr. Charles A. Perera, exemplifies the soundness of his judgment and his vast clinical experience. His ability as an artist is shown in his fundus paintings, and his optical ingenuity, in the design of the earliest electric ophthalmoscope. As a fitting tribute to the impartiality of his professional opinion and character, government agencies, industrial groups, and insurance companies eagerly and frequently sought his advice. Charles H. May was a master in handling patients, for he judged with precision when to give reassurance and sympathy, when to inspire courage, and when to be firm.

In Scotland, a stern and romantic country, where they judge men by what they do and women by what they intend to do, they have an axiom, "The deed will show." Charles H. May's deeds expressed so closely his ideals that they showed him to be among the great teachers and practitioners of ophthalmology.

I thought it fitting to dedicate to the memory of an ophthalmologist with such wide interests a lecture which touched upon the clinical features, pathology, radiotherapy, and surgery of so tragic a disease as retinoblastoma. And so the title of this lecture is Pathological Study of Retinoblastoma Treated by Radon Seeds and Radium Disks.

In general it is true that if the tissue from which the growth arises is radiosensitive, then the neoplasm will also be radiosensitive, and Ellinger (1941) has stated that "tumours arising in radio-resistant tissue are invariably radio-refractory and are to be described as radio-resistant tumours." However, it is fortunate that the latter is not true in the case of retinoblastoma, for although the retina, in common with other parts of the nervous system, is resistant to irradiation, even at doses which are several times more than that which injures blood-forming tissues, the undifferentiated atypical cells of retinoblastoma are highly radiosensitive. So with

Surgeon, the Moorfields Eye Hospital; Ophthalmic Surgeon, St. Bartholomew's Hospital.
The Charles H. May Memorial Lecture.

This paper, in essentially similar form, was published in the *Bulletin of the New York Academy of Medicine* (**30**:132-151 [Feb.] 1954).

Presented, by invitation, before the Section on Ophthalmology, the New York Academy of Medicine, April 20, 1953.

retinoblastoma there is the unique and favorable condition of a very radiosensitive neoplasm arising from relatively radioresistant tissue. The reason that smaller neoplasms are more radiosensitive than larger growths is probably due to the fact that they have a better blood supply. This is certainly so in retinoblastoma. It is evident that radiosensitivity is reduced in anoxemia, and it is greater in the young.

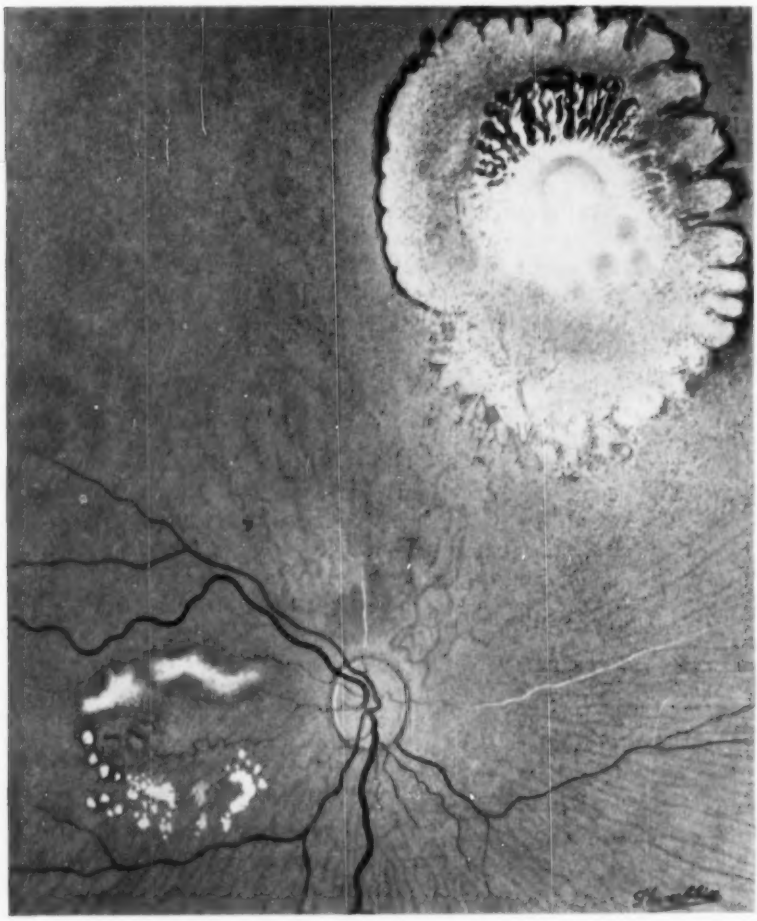


Fig. 1.—Site of irradiated neoplasm in upper nasal quadrant of right eye. Note vascularity of this quadrant, and fine pigment stippling around the characteristic crenated scar.

MATERIAL OF PRESENT INVESTIGATION

I have studied pathologically eight eyes containing irradiated retinoblastoma. Two were completely full of growth and were used in 1930 and 1931 to assess the effective range of a 3.5 mc. radon seed inserted interstitially and left in place for 10 days. One child had a clinical cure of retinoblastoma in the remaining eye, but, unfortunately, died 11 months later of a recurrence in the orbit from which the other, more severely affected eye had been excised.

Another child, one year after successful irradiation of three large masses of retinoblastoma around the optic disc, had an intraocular hemorrhage and complicated glaucoma. Three children had more than half the retina affected by the growth and a total detachment; and there was one patient in whom three-quarters of the retina was involved and who ultimately

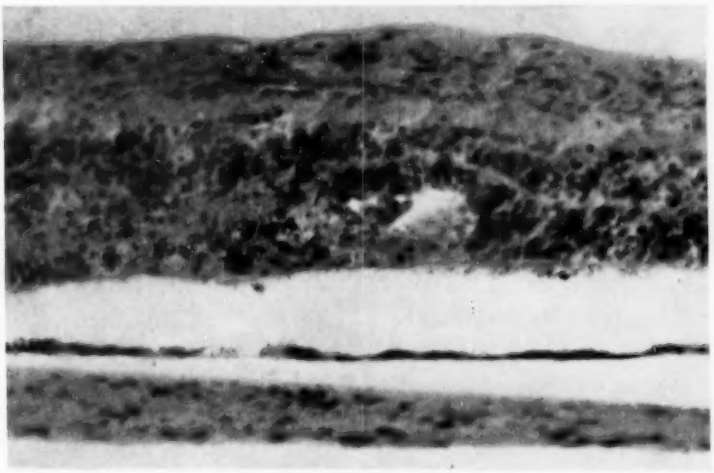


Fig. 2.—Site of retinoblastoma, successfully irradiated. Atrophy and avascularity of the retina and choroid.

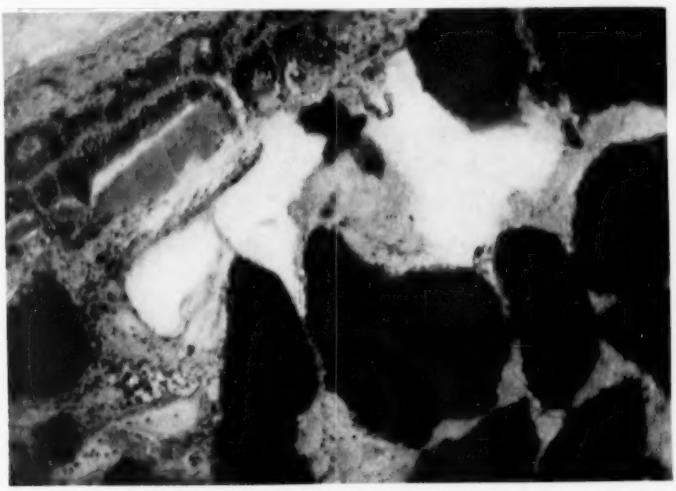


Fig. 3.—Islands of degenerate retinoblastoma cell with no cellular definition.

lost the eye from intraocular hemorrhage and complicated cataract. Serial sections were cut, 16μ thick, and stained with Mallory's phosphotungstic-acid hematoxylin, Feulgen's solution, Heidenhain's iron-hematoxylin, hematoxylin and eosin, Van Gieson's stain, and Hotchkiss' modification of McManus' stain.

Histopathological Changes.—Even though the cell nucleus is no longer regarded as the only radiosensitive component of the cell (the cytoplasm being relatively

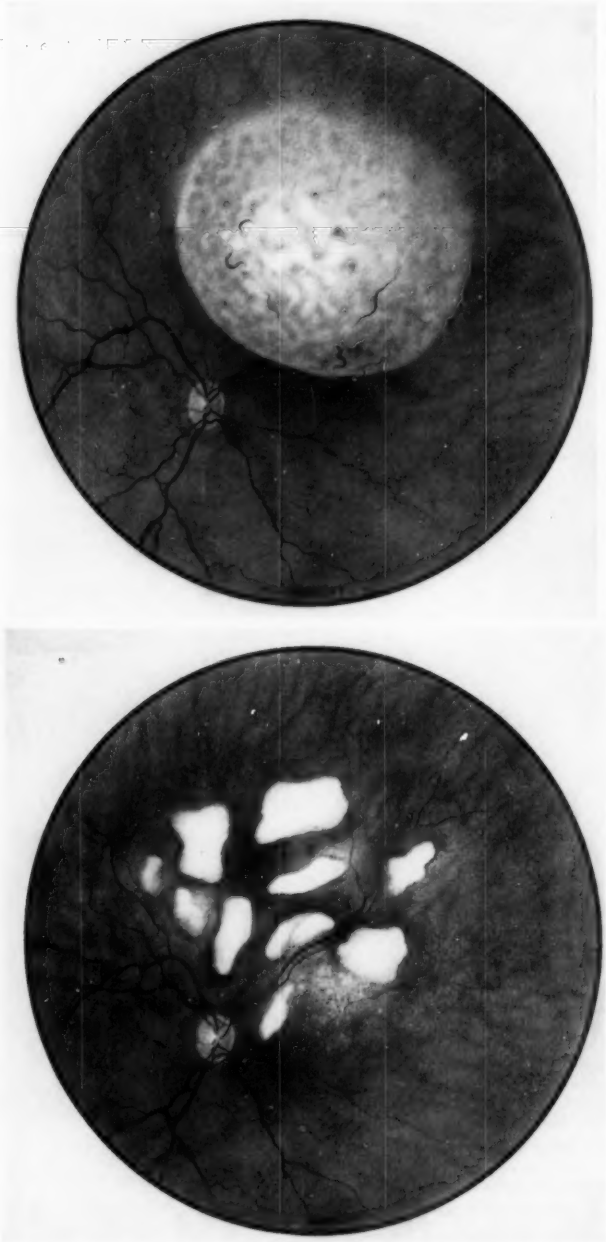


Fig. 4.—*A*, retinoblastoma, upper nasal quadrant, right eye.

radioinsensitive), it is still consistent with modern concepts to regard it as an important indicator of postirradiation intracellular changes and as an expression of radiosensitivity. Nevertheless, it is probable that the nuclear changes are not entirely the result of direct irradiation but may be due also to cytoplasmic changes.

The histological features of an irradiated cell are increase in the size of the nucleus and of the cytoplasm. In the nucleus the chromatin is clumped, broken up into minute spherules, and distributed irregularly around the periphery on the nuclear membrane (pyknosis). In some cases the chromatin granules project from the periphery of the cell as small excrescences. Lobulation is sometimes evident; the nucleoli assume a signet-ring shape; liquefaction occurs, with vacuole formation, and disintegration of the nucleus (karyorrhexis) is followed by its fragments entering the cytoplasm. The cell outline becomes less distinct; vacuolation and increased

Fig. 4 (cont.).—*B*, retinoblastoma shown in *A*, one year after irradiation; *C*, section of white plaques in the retina.

size of the cytoplasm occur. Figure 3 shows these changes in retinoblastoma cells 10 days after interstitial irradiation with a 3.5 mc. radon seed.

Mitosis.—Atypical mitosis is shown by clumping and lagging of the chromosomes and by multipolar asters. Mitosis does not become complete and may remain at the equatorial-plate stage. In the case of those cells which had already begun to divide when radiation struck them the process was completed, but the daughter cells developed into giant cells. Ultimately denaturation of the proteins and their precipitation produce an irreversible change characteristic of irradiation coagulation necrosis in the cell which is radiosensitive. In the case of retinoblastoma it is most likely that this change accounts for the altered ophthalmoscopic appearance of the neoplasm two or three days after irradiation, for its grayish-white, granular appearance changes to a dense white, flocculent mass, from which flakes like curdled milk separate off.

Vascular Changes.—It is evident from both ophthalmoscopic and microscopic examinations that the ultimate fate of irradiated blood vessels is attenuation and the

disappearance of part or all of the vascular tunics. Figure 1 shows these changes on the nasal side, where a retinoblastoma was successfully treated by suturing a radon seed to the sclera. Microscopic examination reveals a deep brilliant pink staining of the collagen of the tunica adventitia, which in cases examined one month after radium or x-ray treatment is a purple pink. Individual collagen fibers become fewer and thicker, and some merge together. Most of the collagen fibers separate and project into surrounding tissues at angles; they are wavy, and some become detached. One week after irradiation these fibers become granular and disappear. In sections examined four to five months after irradiation there is no adventitia. In the tunica media the muscle fibers become swollen and the nuclei enlarge; degeneration occurs late in some cells after high radiation doses, and they ultimately disappear. Nevertheless, muscle and elastic membrane are considered to be radioresistant. The vari-

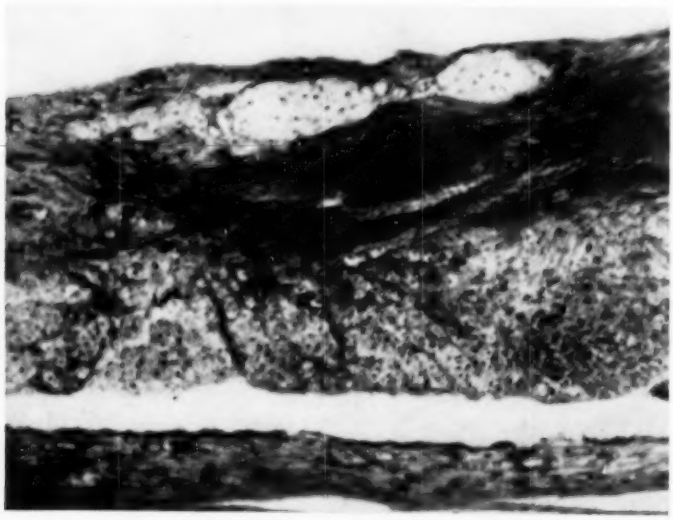


Fig. 5.—"Ghost" cells in ganglion cell layer.

cose appearance and irregularities in caliber of some smaller vessels may be due to compression by changes in the surrounding connective tissue, as well as to the irradiation changes in the vessel wall. In the capillaries, irradiation is said to paralyze the cells of Rouget, to increase their sensitivity to dilator stimuli, and to lessen it for constrictor impulses.

These vascular changes play an important part in the disappearance of the neoplasm. Incidentally, they are also responsible for such late complications as intraocular hemorrhage, radiation cataract, and the slow healing of incisions in the conjunctiva and extraocular muscles when the radium has been placed unavoidably near these structures.

Changes in the Neoplasm.—Figure 2 shows part of the retina which before irradiation was involved in the neoplasm. In this degenerate, disorganized, atrophic area there are no retinoblastoma cells; the neoplasm has completely disappeared. The reduced vascularity of both retina and choroid is obvious.

In some cases traces of neoplastic cells persist in compressed columns and clumps surrounded by fibrous tissue, and in others there are pale-centered islands of degenerate necrotic, and distorted cells, which stain a mauvish-pink color with hematoxylin and eosin (Fig. 3). The central vessel in every island is absent; the cell and nuclear membranes are very faint, and chromatin fragments stain darkly with the basic dyes. Around such islands appear attempts at fibrosis. In one instance (Fig. 4*A*, *B*, and *C*) there were islands of retinoblastoma cells with the nucleus staining well and histologically not necrotic, which remained inactive until the child died of recurrences arising in the orbit of the excised eye nearly a year later. A similar case, in which clumps of retinoblastoma cells remained thus for eight years without proliferation, is reported in the literature.

Calcification occurs in some islands after degenerative changes, and fibrosis around groups of retinoblastoma cells may be the sequel to cellular degeneration and is not specific to irradiation. The swollen "ghost" cells occur in the nerve fiber layer (Fig. 5), on the internal limiting membrane, and in the space between the rods and cones and the retinal pigment epithelium.

At and around the site of irradiation there occurs edema of the retina, which may extend 4 or 5 mm. beyond the periphery of the neoplasm, and in specimens examined up to a year after radium treatment cystic spaces appear in the outer nuclear layer. The periphery of the zone of intense irradiation, where the radon seed or disk has been applied, shows a crenated fringe of coarse broken pigment, which in section is represented by spherical clumps of retinal pigment epithelial cells, and the fine pigment dusting of the retina peripheral to the characteristic irradiation scar is shown by little irregular-shaped deposits of dark and honey-colored pigment in the outer and inner molecular layers and in the ganglion cell layer of the atrophic retina.

Many of the blood vessels disappear, and the larger vessels become attenuated, a feature evident on ophthalmoscopic examination. Some of the vessels are thickened; the nuclei in the structures which form the vascular tunics stain faintly, and hyaline changes are present.

The ganglion cell layer is degenerate, and much of it is replaced by spindle cells, presumably young fibrous tissue, which at some sites projects foward as a small nodule.

In the outer nuclear and molecular layers there are in some specimens irregular-shaped deposits of homogeneous exudate and hyaline material, which stains pink with eosin. The supporting fibers of Müller are distorted at the edge of the neoplasm.

The rods and cones are destroyed, and granular pigmented debris is present between the external limiting membrane and Bruch's membrane. Retinal hemorrhages occur particularly in the ganglion-cell and inner molecular layers. The choroid at and around the site of irradiation becomes thin and atrophic; its vascularity is much reduced, and the choriocapillaries become obliterated. Infiltration of the choroid by retinoblastoma cells is regarded by radiotherapists as a bad prognostic sign. Irradiation cataract is characterized by the so-called "bladder cells" at the equator and in the posterior part of the cortex. In one case the epithelium of the lens capsule completely surrounded it.

It is possible that the destruction of a large mass of retinoblastoma occupying more than half the eye may have produced a toxin which caused ultimately an

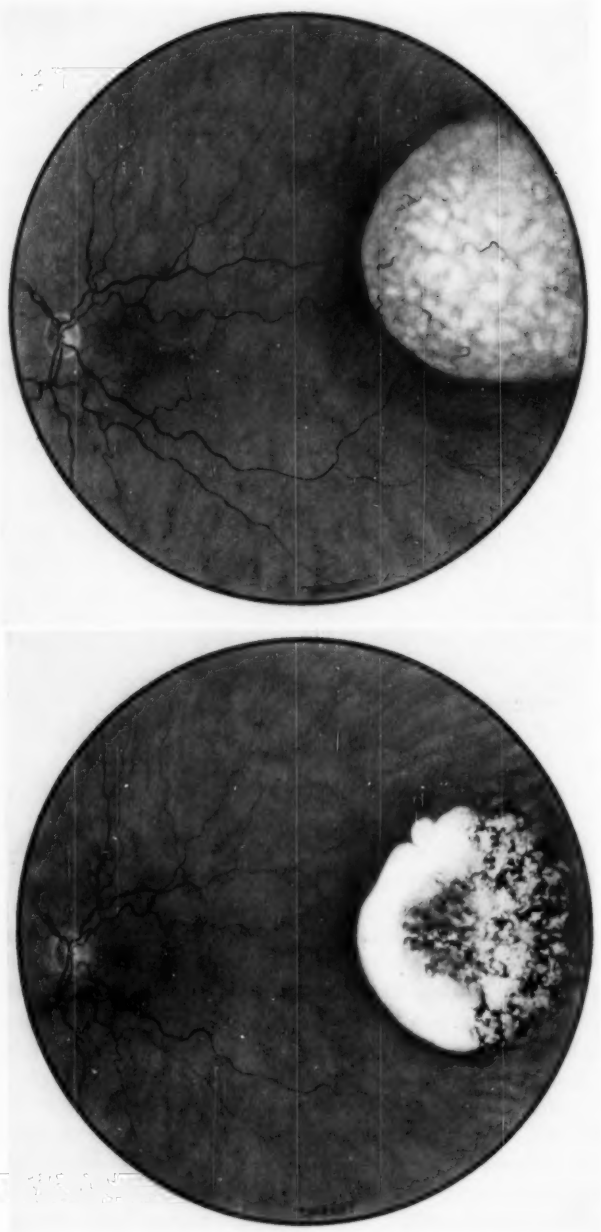


Fig. 6.—*A*, retinoblastoma—nasal side—before irradiation; *B*, after irradiation.

endophthalmitis in one case treated by radon seeds and in two treated with deep x-rays. Iridocyclitis and complicated glaucoma are sequels which are rarer after treatment with radon seeds and radium disks than after deep x-ray therapy. These fundus paintings (Fig. 6*A* and *B*) are typical examples of the changes seen in successfully irradiated retinoblastoma.

CLINICAL STUDY

The statistics, observations, and comments which concern radiotherapy are based on three series of patients.

1. My own series of 36 patients (37 eyes), 16 treated by radon seeds (1934-1948) and 21 by radium disks (1948-1952).

2. Foster Moore's five patients treated by radon seeds (1929-1937).

3. Twenty-five patients treated by other surgeons in the United States, Great Britain, Canada, and Australia.

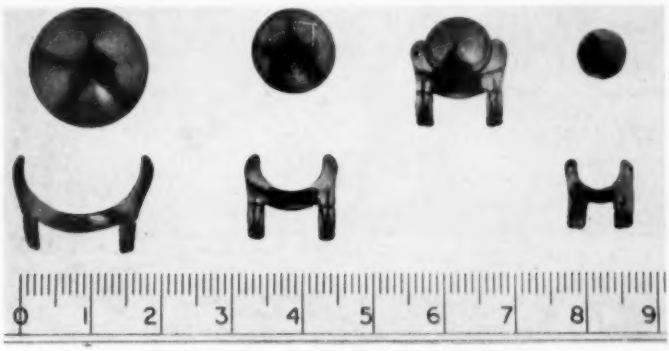


Fig. 7.—Radium disks, 5, 7.5, 10, and 15 mm. active diameter.

Radium Disks.—Since the end of 1948 I have used circular radium disks (Fig. 7) molded to fit the radius of curvature of the sclera exactly, in the belief that these provide a more even irradiation of the neoplasm than the cylindrical radon seeds, which ride at a tangent to the globe. These disks are circular, for the base of a malignant intraocular neoplasm is generally of this shape, and are curved to fit the sclera exactly so as to deliver an even radiation to the underlying growth. The edge of the disk is grooved around its entire circumference, and it fits closely into the groove of a curved semicircular clip, where it is retained by a silk suture which passes through the holes at the ends of each lug and is thence drawn taut in the exposed groove around that part of the disk which is not in contact with the semicircular clip. Two lugs, also curved like the disk, project from the clip; these are either grooved transversely or bored with holes for the retention of the scleral sutures which secure the radium disk and its clip to the eye. The lugs may be of various lengths to facilitate attachment to the sclera by sutures. The platinum casing is 1.3 mm. thick, the inner radius of curvature being 11 mm., the average for the scleral surface in a young child. The wall thickness of the platinum case is 0.5 mm.

and the depth of its cavity 0.3 mm. Within the cavity is either a ring or a ring and central circular disk separated by a short intervening gap, both being made either of asbestos paper impregnated with radium salt, or of cobalt which has been placed in an intense beam of neutrons in the atomic pile at Harwell. Co^{59} captures a neutron to become Co^{60}, which is an unstable atom and disintegrates to nickel, giving off gamma rays and beta particles. Since cobalt and nickel are toxic to tissues, the platinum envelope is sealed hermetically with silver solder. This distribution of

Details of Radium Disks

Active Diameter, Mm.		
5.0	Co^{60} ring	5.0 mm. O.D. 1.75 mm. I.D. 0.2 mm. thick
7.5	Co^{60} ring	7.5 mm. O.D. 1.75 mm. I.D. 0.2 mm. thick
10.0	Co^{60} ring	9.75 mm. O.D. 6.25 mm. I.D. 0.2 mm. thick
	Co^{60} disk	2.0 mm. diameter 0.2 mm. thick
15.0	Co^{60} ring	15.0 mm. O.D. 11.5 mm. I.D. 0.2 mm. thick
	Co^{60} ring	9.0 mm. O.D. 5.0 mm. I.D. 0.2 mm. thick
	Co^{60} disk	2.0 mm. diameter 0.2 mm. thick

Construction of Radium Disks
1 Mc. Co^{60} 1.43 Mg. Radium

Active Diameter, Mm.	Outside Diameter, Mm.	Maximum Depth of Lesion, Mm.
5.0	7.0	4.0
7.5	9.75	6.5
10.0	12.0	8.0
15.0	17.0	11.5

Active Diameter, Mm.	Co^{60} Required, Mc.	At 2 Mm. from Surface of Applicator, r
5.0	0.63	19,000
7.5	1.0	19,000
10.0	1.46	19,200
15.0	3.15	19,000

either the radium or the irradiated cobalt is designed to make the dose as uniform as possible at the curved surface of the retina. The 0.5 mm. thick platinum case absorbs alpha and beta radiation, so that only gamma rays reach the tissues. Disks from 5 to 15 mm. in diameter are used, and their radium content ranges from 0.63 to 3.15 mc. Co^{60} (Table). The radium loading has been calculated to give a dose of approximately 3,500 r in one week (168 hours) at the apex of the neoplasm. For this purpose, the height of the growth has been assumed to be seven-tenths of its diameter (Fig. 8). The half-life of an irradiated cobalt disk is 5.2 years, and in view of this decay rate the dose has to be adjusted at least once a year.

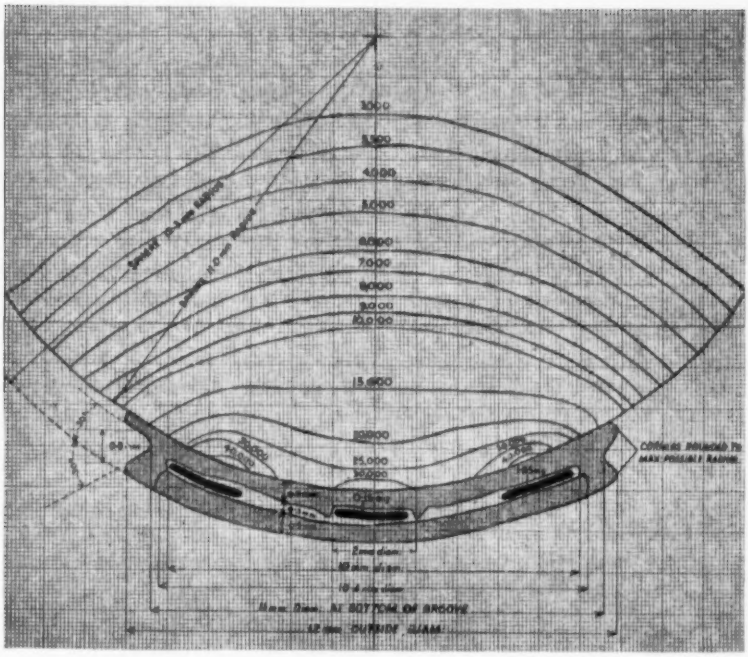


Fig. 8.—Isodose curves for radium disks of 10 mm. active diameter.

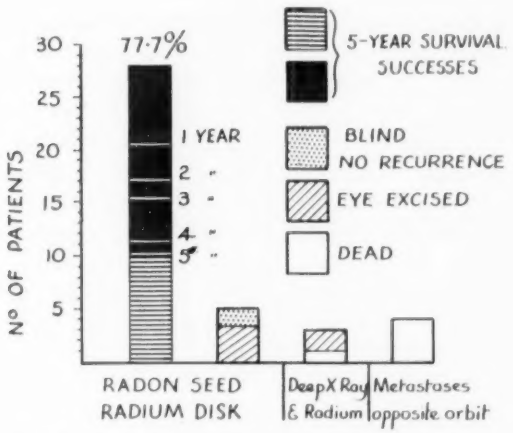


Fig. 9.—Results in my own series, of 36 patients (37 eyes).

CLINICAL FACTS

Series 1.—Of the 36 patients (37 eyes, Fig. 9) treated by radon seeds and radium disks in my own series, 28 have kept some useful vision, and there has been no evidence of recurrence in the irradiated eye. Ten of these 28 patients are still alive, more than five years after irradiation, their periods of survival being 18 years (one), 17 years (one), 16 years (one), 15 years (one), 14 years (two), 13 years (one), 6 years (one), and 5 years (two). Of the seven failures who are all blind but still alive, two have kept their remaining irradiated eye with no sign of recurrence (one for 15 years and the other for 13 years) since the application of radon seeds. In five cases the irradiated eye has been excised—because of total detachment in two, vitreous hemorrhage and complicated glaucoma in two, and vitreous hemorrhages and retinal detachment in another. Microscopic examinations of serial sections of these eyes showed no clear histological evidence of active retinoblastoma cells. For the three patients who were given deep x-rays and then radium the prognosis was unfavorable, for more than half the retina had already been destroyed by the neoplasm and the remainder was detached. The therapeutic intention in these advanced cases was to destroy as much of the growth as possible by deep x-rays and then to deal with any remaining localized active residue with a radium disk, in the vain hope that the perception of light which seemed to exist in the detached retina would give the child some measure of guiding vision. These three cases were ultimately failures, necessitating excision of the eye one and a half to two years after treatment on account of intraocular complications. There was a severe vitreous hemorrhage and complicated glaucoma in two cases, and in the third there occurred endophthalmitis, possibly excited by toxins from a mass of cells destroyed by irradiation. In two of these cases, however, there was no certain evidence on microscopic examination of serial sections that any active retinoblastoma cells remained. Four patients who had the neoplasm in their remaining eye successfully treated (one by radon seeds and the other three by a radium disk), three of whom had good vision with an unaffected macula and a healthy-looking optic disc for one to two years, died of a recurrence in the orbit of the excised eye, the recurrences having been unsuccessfully treated by deep x-rays in each case. It is probable that the proper action to take in such cases is immediate exenteration of the socket followed by deep x-ray treatment (in Reese's series an orbital recurrence was fatal in every case in which it occurred). In the successfully irradiated eyes the visual acuity is now as follows:

	No. of Cases
6/6	6
6/9.6/6 partly (edge of macula scarred)	1
6/9	1
6/18	2
6/24 where the macula was involved in the growth	1
With aphakia and perimacular exudates	1
6/36 where the macula was involved in the growth	1
6/60 with neoplasm situated at the macula	2
1 also had central lens opacities	
Perception of light	1

The remaining eight patients, one of whom had both eyes irradiated, are still too young for any reasonable estimate of their vision to be made. In four of these it should be reasonably good. It is remarkable that four patients with the scar of the successfully irradiated neoplasm obliterating the papillomacular region have been able to use the nasal part of the retina to read. One boy reads J4 and draws most accurately.

Complications: The reasons for the failures which resulted in loss of sight and excision of the irradiated eye have been stated as total retinal detachment, complicated glaucoma, and severe intraocular hemorrhage. Such complications occurred in eyes in which more than half the retina was destroyed by the neoplasm, and in which three or more large islands of growth were near the optic disc. The complications in those cases classified as unsuccessful with some preservation of sight were as follows:

1. Cataract necessitated the extraction of the lens in three cases. A small opacity about 1.5 mm. in diameter has remained stationary in the center of the posterior cortex in three cases and at the equator in the upper nasal quadrant in one case. In six cases the opacity followed the use of radon seeds, and in one, in which a 0.63 mc. Co^{60} radium disk was applied between the equator and the ora serrata, a small posterior cortical opacity has appeared. It is probably still too early to judge whether the incidence of radiation cataract will be affected by the radium disk technique, which I have used only since the end of 1948. In five cases the opacity followed the application of three or four 2-mc. radon seeds, and in one case it occurred after the use of one 2-mc. seed placed between the equator and the macula. In three cases in which the lens became so opaque that discission and curette evacuation were necessary, the radon seeds had been placed just behind the equator; in two in which there was a small central posterior cortical opacity, the seeds had been sutured to the sclera over the macula. The earliest onset of lens opacification was 10 months after the application of a 0.63-mc. Co^{60} radium disk, and the longest 11 years 6 months after three 1.1-mc. radon seeds had been applied over the macula.

2. Retinal exudates, resembling circinate retinopathy, were present at and around the macula in three patients who had radon seeds applied behind the equator. These exudates appeared from 7 months to 9 years after irradiation and have persisted for 11 years.

3. Retinal hemorrhages on a small scale occurred in three cases. In one these appeared 3 years 1 month after irradiation of the macula and have persisted for 13 years; in another a small retinal hemorrhage occurred adjacent to the optic disc one year after the application of a 2-mc. radon seed to the macula; in the third a hemorrhage over the irradiated papillomacular area appeared when the patient was 14 years old, or 13 years after irradiation.

4. White sheathing of larger branches of retinal vessels around the optic disc and pallor of the disc occurred in two cases after the application of a radium disk behind the equator.

5. Diffuse choroidal and subretinal hemorrhage occurred seven months after the use of a 1.46 mc. Co^{60} radium disk to irradiate a large mass around the macula and optic disc. This hemorrhage absorbed in three months.

Series 2.—In Foster Moore's series of five patients (Fig. 10) treated between 1929 and 1937, four have survived. Two of these had irradiation cataract but sufficient vision, despite aphakia and macular scarring, to enable them to earn a living; two are blind, one from endophthalmitis following interstitial insertion of three 3.18-mc. radon seeds, and the other from severe intraocular hemorrhage, iridocyclitis, and complicated glaucoma, which occurred 11 months after successful irradiation. One died of gastroenteritis during postoperative convalescence.

Series 3.—I have collected 25 additional cases reported in the literature by other surgeons (Fig. 10). In these cases, as in Foster Moore's series, most of the successes were obtained by radon seeds. Of the seven successes, three are still alive five years after treatment and the vision is from 6/6 to 5/60. Of the four failures, one died of metastases, two became blind from total retinal detachment, and one received too much radiation for the eye to retain any useful function. In some hospitals a variety of techniques has been used, including the insertion of radium needles and

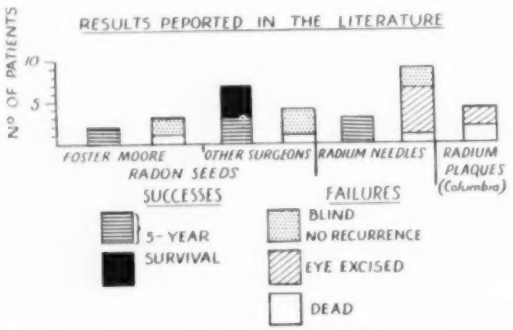


Fig. 10.—Results in Series 2 and and 3 (Foster Moore and other surgeons).

radon seeds into the orbit unfixed around the site of the intraocular neoplasm or at intervals around the eye, and the external application of Columbia paste plaques containing radium needles. It is clearly evident that the insertion of radium needles into the orbit damaged the eye so considerably that useful vision was lost in 7 out of 10 patients treated by this technique. The points of the needles converged to make a truncated cone, with its anterior diameter about 3 cm. and its sides 1.5 to 4.5 cm. long, depending on the active length of the needle. In some cases four needles were also disposed as a coronal frame in the orbit about the plane of the equator of the eyeball. The distribution of the needles was made regardless of the site of the retinoblastoma, which in six instances occupied less than one quadrant of the eye and in another case was at the papillomacular area and measured 6 by 4.5 mm. The needles were left in place for seven days in most cases, the least time being four days and the greatest nine days.

After this treatment three children have some imperfect vision. Of the seven failures, one is blind in both eyes, which he has retained, five have had their blind eyes removed (one of these had both eyes irradiated and subsequently excised), and one whose eye was reported to be full of retinoblastoma died after an orbital recur-

rence. The cause of failure in seven eyes has been severe intraocular hemorrhage and retinal detachment, and in another patient it is likely that behind the irradiation cataract in both eyes there is gross destruction of the retina, for there is no perception of light in either eye. In six of these cases the neoplasm was small enough and was so situated that in my opinion the visual prognosis should have been good with appropriate irradiation applied to the base of the neoplasm.

The results of using Columbia paste plaques holding radium needles were quite disastrous in every case, since they failed to destroy even small islands of retinoblastoma. Of the four patients treated by this Columbia paste plaque technique, two died of metastases and two were blinded by dense vascularized opacification of the cornea. One child also suffered distortion of the upper lid and trichiasis. The tragedy

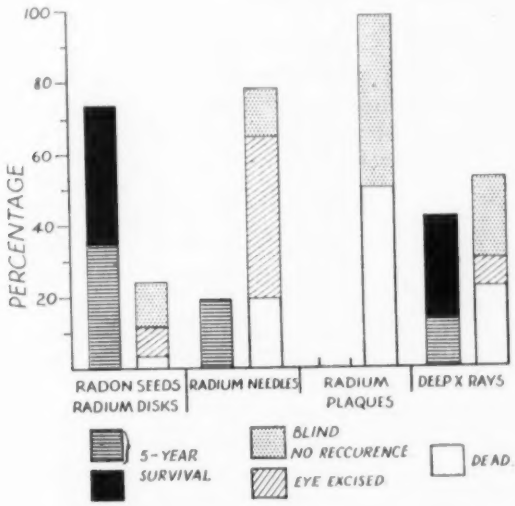


Fig. 11.—Comparative results with different methods of treatment.

is that in 13 children treated by radium needles either inserted into the orbit or implanted in Columbia paste plaques the islands of neoplasm were small and should have responded to treatment by either a radon seed or radium disk fixed to the sclera at the appropriate site.

A radioactive tantalum wire doubled to form a rectangular frame was used in one case, but the patient lost perception of light, owing to iritis, irradiation cataract, and retinal detachment from too much irradiation.

FOLLOW-UP

While small neoplasms under 5 mm. in diameter may disappear within three or four weeks after irradiation, with larger growths, when one quadrant or more has been affected, it is generally necessary to wait at least two months before it is possible to assess the maximum effect of irradiation.

CONCLUSIONS

A study of these cases has made it clearly evident that when one-third or less of the retina is involved in a retinoblastoma there is reasonable hope that it may be destroyed by radiation therapy. With very few exceptions, the results are bad when one-half or more of the retina is already destroyed. In such cases retinal detachment is generally present, or, if it is not already so, will almost certainly occur after irradiation. Later sequalae are severe intraocular hemorrhage, iridocyclitis, complicated glaucoma, and endophthalmitis. Irradiation often fails when the choroid is infiltrated. It would therefore seem advisable in such advanced cases to excise the eye with 10 mm. of the optic nerve and to give postoperative irradiation to the orbit. In no instance in this series was irradiation of the eye worth while when half or more of the retina was involved in the growth.

The dose is still empirical. It is a fact that the neoplasm in some patients is more radiosensitive than in others, and I think it is evident that the retinoblastoma is more radiosensitive than the more highly differentiated neuroepithelioma. It seems that a dose of 2,500 to 3,500 r at the summit of the neoplasm is generally effective.

In my opinion it is desirable to bring the therapeutic artillery as close as possible to the target and to hit hard and quickly, with a concentration of fire that is known to be both effective and reasonably safe for the eye. To achieve this, I think that radium disks made to fit the scleral curvature evenly are better than radon seeds and the other applicators so far used. This technique is preferable to long-range shooting by heavy doses from radium needles fixed in Columbia paste plaques or from the radium "bomb," for both these methods are disastrous for the eye and are often quite ineffective in destroying the neoplasm.

Although deep x-ray treatment is successful in many cases, in which less than one-third of the retina is affected by the neoplasm, it has the technical disadvantages of protracted treatment and the difficulty of maintaining the necessary immobility of a child's head, and it also produces a higher incidence of serious complications than follows the application of either a radium disk or a radon seed.

Figure 11 gives a comparison of the results of various methods of irradiation. It includes statistics taken from Reese's classical work on deep x-ray therapy. These statistics are based on as large a collection as I could obtain from the literature. It is evident that the results of treatment by radon seeds and radium disks in several series in which the size of the retinoblastoma was fairly comparable are appreciably better with this technique than the others.

BIOCHEMISTRY OF THE EYE

I. Chromatographic Investigation of Free Amino Acid Constituents of Vitreous Humor

JOHN F. WOOTTON, M.S.
ROGER G. YOUNG, Ph.D.
AND
HAROLD H. WILLIAMS, Ph.D.
ITHACA, N. Y.

NO DETAILED analysis of the free amino acid content of the vitreous body has been reported. Duke-Elder [1] reported a total value, and Krause [2] determined the basic amino acids of the vitrein and mucoid portions of the vitreous. More recently Schaeffer and Murray [3] recorded the results of microbiological assays of the whole vitreous protein. In view of the paucity of detailed knowledge of the amino acids in the vitreous and their role in the chemical structure of that body, this report presents results of ion exchange chromatographic analysis of the amino acids which occur free in the vitreous humor.

MATERIALS AND METHODS

Bovine eyes were obtained from a meat-packing plant. Within four to eight hours after removal of the orbs from the freshly killed animal, the vitreous was separated and filtered by gravity. The filtered liquid was stored for short periods at 4 C. and in the frozen state for longer periods.

Several methods for preparing the filtered vitreous for chromatography were used. For good resolution of the amino acids, it was imperative to remove extraneous material prior to placing the samples in the column.

Treatment with hot 80% ethanol is a common means of removing protein. Bulky precipitates were obtained from vitreous in this way. However, after filtration and concentration, it was noted that the separation of aminoacetic acid from alanine and serine from threonine was incomplete.

Trichloroacetic acid in a final concentration of 10% w/v did not immediately precipitate material from fresh vitreous filtrates. The colloidal suspension formed was extracted as an emulsion with ether, leaving a clear water layer, which after appropriate concentration yielded a well-separated amino acid pattern. This method was used for Samples 1 and 2.

Material for Sample 3 was prepared by mixing 400 ml. of 95% ethanol with 100 ml. of vitreous filtrate, boiling briefly, filtering off the precipitate, and evaporating the alcoholic solution to 5 ml. Immediately before chromatography a portion was made to 10% with trichloroacetic acid and the precipitate removed by centrifugation. The amino acids in the clear supernatant were well resolved on the columns.

The acidic and neutral amino acids were separated by passage through a 100×0.9 cm. column of Dowex-50 ion exchange resin. The basic components were analyzed on a 15×0.9 cm. column. The chromatographic technique described by Moore and Stein [4] was used throughout. One-milliliter fractions of the column effluents were collected by means of an automatic drop-counting fraction collector and analyzed by the ninhydrin method of Moore and Stein.[5]

From the School of Nutrition and the Department of Biochemistry and Nutrition, Cornell University.

Supported in part by grants to Cornell University by William C. Geer and the Herman Frasch Foundation.

The color equivalent of each amino acid was determined experimentally and was used to calculate the amount of each amino acid. Where partial overlapping of peaks occurred, the amount of each component in the overlap was calculated graphically.

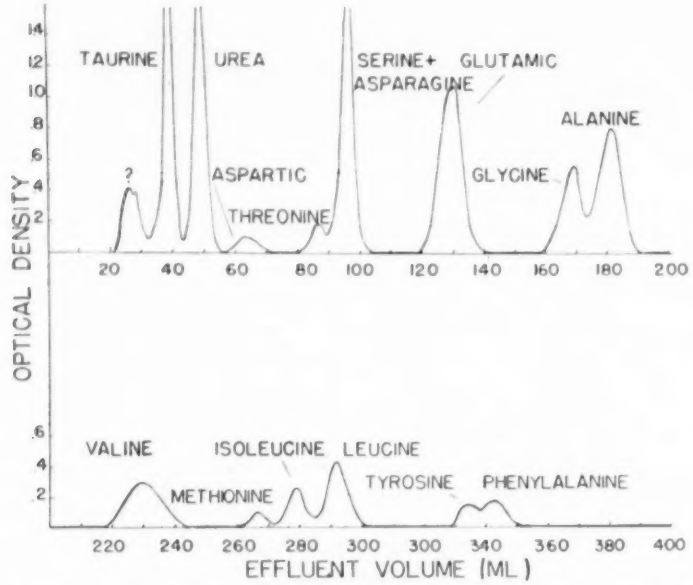


Chart 1.—Chromatographic separation of the acidic and neutral free amino acids of vitreous humor with a column of Dowex-50, 0.9 × 100 cm.

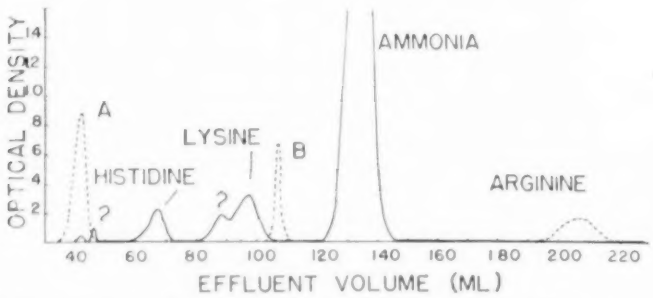


Chart 2.—Chromatographic separation of the basic free amino acids of vitreous humor with a column of Dowex-50, 0.9×15 cm. Peak *A* (dotted line) represents unknown appearing after hydrolysis. Peak *B* and arginine (dotted lines) are present after special isolation treatment. See text for details.

RESULTS

The amino acid pattern of Sample 1 is shown by the solid line in Charts 1 and 2. The optical density of the ninhydrin complex of the amino acids is plotted against the volume of effluent from the column. The area under the peak, after correction

for the color value of the particular amino acid, represents the amount present in the sample. The identity of the peaks labeled in Charts 1 and 2 was established by combinations as follows:

1. A mixture of amino acids suspected to be present was chromatographed after mixing with a vitreous extract. The appropriate peaks rose in height relative to the normal pattern without developing asymmetry.

2. Acidic and neutral amino acids isolated by passage through a 100 × 2.8 cm. column were chromatographed on paper. The unknowns were identified by comparison with adjacent spots of known amino acids and by using mixtures. There was no separation of the mixtures, and the *Rf* values were the same as of those of the known spots.

Free Amino Acid Content of Bovine Vitreous Humor and Blood Serum, in Milligrams per 100 Ml.

Amino Acid	Vitreous Humor			Blood Serum, Sample 4
	Sample 1	Sample 2	Sample 3	
Taurine	2.4	1.5	2.3	0.7
Aspartic	0.2	...	0.2	0.1
Threonine	0.3	0.2	0.8	0.7
Serine	0.9	0.8	1.8	1.4
Asparagine	0.9	0.8	1.8	1.4
Glutamic	2.9	4.0	0.6	1.3
Aminoacetic	0.7	0.6	0.6	2.4
Alanine	1.2	1.3	1.3	2.5
Valine	1.0	1.8	1.6	2.2
Methionine	0.2	...	0.1	0.2
Isoleucine	0.5	0.9	0.9	0.8
Leucine	0.9	0.9	1.4	1.6
Tyrosine	0.4	...	0.8	0.5
Phenylalanine	0.6	...	1.0	1.2
Histidine	0.4	0.2	0.3	0.3
Lysine	0.8	0.4	0.2	0.3
Arginine	...	...	1.1	...

3. An aliquot of a vitreous preparation was hydrolyzed with 6 N HCl for 16 hours. The peaks of the hydrolyzed material were qualitatively unchanged. All the amino acid peaks increased except serine and asparagine.

The results with Sample 2 were in substantial agreement with those with Sample 1. A portion of the material from Sample 2 was chromatographed after hydrolysis with 6 N HCl for 16 hours. The total ninhydrin value of the sample increased 2.5 times, and a new, unidentified peak, marked *A* in Chart 2, appeared. It was by means of the above hydrolysis that the values for serine and asparagine were determined. Serine and asparagine almost completely overlap, under the conditions used. The hydrolyzed material contained only serine. The difference before and after hydrolysis, therefore, allowed calculation of the asparagine value. The ratio of serine to asparagine as determined by this procedure was then used to calculate the amount of each acid present in the other analysis.

Sample 3 showed several differences from the samples prepared by trichloroacetic acid alone. First, the serine-asparagine and threonine peaks were increased, and that of glutamic acid was markedly decreased. Second, an unidentified peak, marked *B* in Chart 2, appeared after lysine. Third, arginine was found, possibly

because the sample was in contact with trichloroacetic acid for only a few minutes before being chromatographed. Arginine was also apparent in material prepared with ethanol as the only solvent.

A consistent finding was a series of overlapping peaks at the beginning of the acid column. They have not been identified. Paper chromatography indicated four ninhydrin-reactive constituents, one of which gave a red color with the reagent. Other recurrent, but as yet unidentified, peaks are noted by question marks in the Charts. Similar results were noted by Stein[6] in urine. Tryptophan, if present at all in vitreous preparations, occurs in very low concentration. No evidence for the presence of cystine was found.

Quantitative results, calculated for the three vitreous samples, are presented in the Table, together with the results of a sample of bovine serum trichloroacetic acid filtrate (Sample 4).

CONCLUSIONS

The analyses reported in this investigation support the view that the amino acids present in the vitreous humor represent an ultrafiltrate of blood, although the relative concentration tends to be lower. Some qualitative and quantitative differences in the amino acid patterns of vitreous filtrates prepared for chromatographic analysis by different methods were found. In addition to 17 known amino acids, the presence of several as yet unidentified ninhydrin-reactive substances in the vitreous has been revealed.

Drs. Norman S. Moore and L. A. Maynard gave advice and criticism throughout the course of this investigation.

REFERENCES

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 1, St. Louis, C. V. Mosby Company, 1932, p. 428.

2. Krause, A. C.: Chemistry of the Vitreous Humor: I. Chemical Composition of the Proteins, Arch. Ophth. **11**:960, 1934.

3. Schaeffer, A., and Murray, J.: Amino Acid Composition of the Tissue Proteins of the Cornea, Sclera, Vitreous, and Retina, Arch. Ophth. **44**:833, 1950.

4. Moore, S., and Stein, W. H.: Chromatography of Amino Acids on Sulfonated Polystyrene Resins, J. Biol. Chem. **192**:663, 1951.

5. Moore, S., and Stein, W. H.: Photometric Ninhydrin Method for Use in the Chromatography of Amino Acids, J. Biol. Chem. **176**:367, 1948.

6. Stein, W. H.: A Chromatographic Investigation of the Amino Acid Constituents of Normal Urine, J. Biol. Chem. **201**:45, 1953.

BIOCHEMISTRY OF THE EYE

II. Gelatinous Protein of Vitreous Body

ROGER G. YOUNG, Ph.D.
AND
HAROLD H. WILLIAMS, Ph.D.
ITHACA, N. Y.

OF THE proteins which are present in the vitreous body, the gelatinous material seems to be most significant. It has been termed vitrein,[1] or residual protein,[2] and a recent preparation of the structural protein has been called vitrosin.[2] Krause [1] purified the protein by filtration, followed by treatment with papain, and recorded some data on its chemical properties. It was the purpose of this investigation to prepare the gelatinous protein of the vitreous, by methods calculated to preserve its native state as much as possible, and to determine, in part, its chemical composition.

METHODS

Vitreous bodies from freshly killed cattle were removed and placed on a Buchner funnel without filter paper. Very gentle stirring with a horizontal glass rod allowed the viscous liquid to drain through. About 90% of the original volume was removed, leaving a thick gel.

Inevitably, some denaturation occurred during filtration. The opalescent fibers so formed collected on the stirring rod and were cut away with scissors and discarded. The transparent mass was transferred to a large flask, which was filled with approximately 10 times the gel volume of water. The flask was layered with toluene and kept at 4 C. The water was replaced by decanting and refilling at twice-weekly intervals for 12 to 20 weeks. After this interval no solids were present in the washings. The twice-weekly interval allowed ample time for diffusion of impurities from the gel. Two preparations of vitreous gel were treated for 24 hours with papain, activated by cysteine, prior to the washing procedure. One preparation of vitreous gel was treated with bull testes hyaluronidase for 24 hours before washing.

To insure accurate sampling for analysis, the vitreous proteins were homogenized in a Waring Blendor before being dried from the frozen state. The protein as prepared by washing makes up 0.03% by weight of the fresh vitreous body. The accompanying Table presents analytical figures for nitrogen and carbohydrate of the prepared proteins and the amino acid distribution of the washed protein.

Total nitrogen was done by the micro-Kjeldahl method. Carbohydrate was determined by means of the anthrone reagent. The amino acid composition of the washed untreated protein was determined by the chromatographic technique of Stein and Moore.[3] Hydrolysis prior to chromatography was carried out with glass-distilled 6 N HCl for 16 hours in a sealed tube at 110 C.

COMMENT

The Figure shows photographs of the gel protein after 10 weeks' washing. The untreated vitreous remained intact throughout the washing period, with development of only a slight opalescence. The hyaluronidase-treated material became somewhat opaque and fibrous during incubation and remained unchanged during the

Supported in part by a grant to Cornell University by William C. Geer.

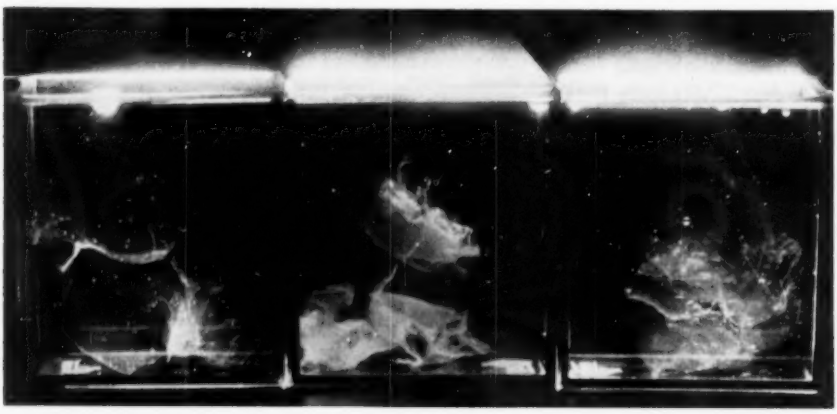
From the School of Nutrition and the Department of Biochemistry and Nutrition, Cornell University.

washing. The material incubated with papain became uniformly opalescent. During the washing period it fragmented and the gel structure became less rigid. After lyophilization it showed no evidence of the tough fibers which were present in the untreated and hyaluronidase-treated proteins.

*Composition of the Gel Protein of the Vitreous Body**

	Washed Protein, %	Papain Treated and Washed, %	Hyaluronidase Treated and Washed, %
Nitrogen	13.4	12.5	13.6
Carbohydrate	4.5	3.8	4.3
Ash	1.0	....	....
Amino acids (gm./100 gm. dried protein)			
Hydroxyproline	15.4	....	....
Aspartic acid	6.3	....	....
Threonine	2.2	....	....
Serine	2.3	....	....
Glutamic acid	1.2	....	....
Proline	8.4	....	....
Aminoacetic acid	18.0	....	....
Alanine	2.2	....	....
Valine	2.6	....	....
Isoleucine	1.8	....	....
Leucine	5.4	....	....
Tyrosine	0.8	....	....
Phenylalanine	1.9	....	....
Tryptophan	1.1	....	....
Histidine	2.6	....	....
Lysine	2.4	....	....
Arginine	5.3	....	....

* Phosphorus and hexosamine were not detected.



The appearance of the gelatinous protein of the vitreous humor after washing, with and without prior enzyme treatment.

The cell on the left contains vitreous gel after 10 weeks of washing. The cell in the center contains gel which was treated with papain prior to washing. The cell on the right contains gel which was treated with hyaluronidase prior to washing. The white spots are due to trapped air bubbles.

It appears, therefore, that the papain had some degrading effect on the vitreous gel proteins. The lower nitrogen and carbohydrate values for the papain-treated material indicated a more effective binding of water.

CONCLUSIONS

The preparation of the gelatinous protein of the eye by gentle methods is described. The use of papain to remove extraneous protein causes some alteration of the protein, as judged from the appearance and analysis of the gel. The ash-free material obtained by repeated washing of the vitreous gel showed an amino acid pattern similar to that of gelatin in that high proportions of aminoacetic acid, proline, and hydroxyproline were found. No methionine was detected.

Drs. Norman S. Moore and L. A. Maynard gave advice and criticism throughout the course of this investigation.

REFERENCES

1. Krause, A. C.: Chemistry of the Vitreous Humor: II. Chemical Composition of the Proteins, Arch. Ophth. **11**:960, 1934.

2. Mataltsy, A. G.: Structural Protein of the Vitreous Body, J. Gen. Physiol. **36**:29, 1952.

3. Wootton, J. F.; Young, R. G., and Williams, H. H.: Biochemistry of the Eye: I. Chromatographic Investigaion of Free Amino Acid Constituents of Vitreous Humor, A. M. A. Arch. Ophth., this issue, p. 589.

BIOCHEMISTRY OF THE EYE

III. Lipids of the Lens, Cornea, Iris, Ciliary Body, and Retina

BARBARA S. D'ASARO, M.N.S.
ROGER G. YOUNG, Ph.D.
AND
HAROLD H. WILLIAMS, Ph.D.
ITHACA, N. Y.

IN STUDIES * of the vitreous humor it was noted that little, if any, lipid material was present. A review of the literature revealed extensive but questionable quantitative information on the lipid content of different parts of the eye. For the most part, the data that are available were obtained before the development of the present, more reliable techniques for extracting and fractionating the several types of lipids present in tissues.[3]

Consequently, the present report deals with the quantitative evaluation of various lipid fractions in different parts of the eye.

MATERIAL AND METHODS

Eyes from freshly killed cattle were obtained at a nearby packing plant. They were transported to the laboratory in gallon Thermos jugs containing cracked ice. The various parts were dissected immediately and dried from the frozen state. The dried material was ground in a micro-Wiley mill and redried in a desiccator.

The dried samples were suspended in ethanol-ether (3:1) overnight, and the residue was further extracted for 15 to 20 hours in a Soxhlet flask, first, with 95% ethanol and, second, with ether. The combined extracts were evaporated, and the lipids were dissolved in a known volume of petroleum benzin U. S. P.-chloroform (7:1) for analysis.

Total fatty acids and cholesterol were determined by a modification of the method of Bloor.[4]

Phospholipids were estimated from the total lipid-soluble phosphorus. The latter was determined, after conversion to inorganic phosphate, by the method of Sumner.[5] The factor of 25 was used to convert the lipid-soluble phosphorus to phospholipid on the basis that mixed tissue phospholipids contain approximately 4% phosphorus.

Choline-containing lipids (lecithins and sphingomyelins) were estimated from the total lipid-soluble choline. The latter was determined by a modification of the method of Glick.[6] The factor of 6.65 was used to convert the lipid-soluble choline to choline-containing lipid on the basis that mixed tissue choline-containing lipids contain 15.03% choline.

Cholesterol was determined by the method of Sperry and Webb.[7]

From the School of Nutrition and Department of Biochemistry and Nutrition, Cornell University.

* References 1 and 2.

RESULTS

The results are presented in the accompanying Table. It is evident that cholesterol and phospholipids comprise most of the lipids found in the tissues studied. Cholesterol is present in the free form, inasmuch as no significant amounts of esterified cholesterol could be detected. Phospholipid accounted for over 80% of the fatty acids except in the cornea. The choline-containing lipids (lecithins and sphingomyelins) account for over 50% of the total phospholipid except in the lens.

Although the exact function of the various types of lipids is still unknown, their general physiological significance has been amply demonstrated. The phospholipids in conjunction with cholesterol reflect the "essential lipid" content of a tissue [8] and as such give "an expression or a measure of the extent and variety of the physiological activities of that tissue." [9] Consequently, the lens and the cornea have relatively low physiological activity in comparison with the other tissues studied. This does not imply that they lack equal importance to the eye as an instrument of vision. It does indicate, nevertheless, that these particular tissues, the lens especially, are

*Lipid Content of Various Parts of the Eye**

Eye Tissue	Total Fatty Acids and Cholesterol	Cholesterol	Fatty Acids†	Phospholipids				
				Total	Choline-Containing		Fatty Acids‡	
					Amount	Per Cent of Total	Amount	Per Cent of Total
Lens	0.80 (0.69-0.89)	0.26 (0.22-0.30)	0.54	0.65 (0.53-0.86)	0.29 (0.25-0.32)	45	0.44	82
Cornea	1.45 (1.39-1.52)	0.43 (0.36-0.52)	1.02	1.07 (0.95-1.24)	0.76 (0.62-0.98)	71	0.72	70
Retina	2.86 (2.58-3.02)	0.65 (0.61-0.67)	2.21	2.72 (2.66-2.85)	1.40 (1.15-1.58)	51	1.82	82
Iris	3.23 (2.99-3.64)	0.67 (0.56-0.78)	2.56	3.94 (3.49-4.30)	2.23 (2.08-2.38)	57	2.64	100
Ciliary body	4.25 (3.38-4.90)	0.76 (0.61-0.85)	3.49	5.23 (4.80-5.85)	3.19 (2.84-3.72)	61	3.50	100

* Expressed in per cent of dry weight except where noted. Figures in parenthesis are the range of values obtained on three or more samples obtained at different times. They are given for the directly determined values only. All other values have been calculated from these.

† Total fatty acids equal the difference between Columns 2 and 3.

‡ Phospholipid fatty acids equal total phospholipids times the factor 0.67, on the basis that two-thirds of the phospholipids is fatty acid.

relatively inert metabolically, in comparison with such tissues as the retina, iris, and ciliary body. It may be of further significance to note here that the vitreous humor, as pointed out earlier, was found to contain little, if any, lipid material.

CONCLUSION

Partial fractionation of the lipids in various portions of the eye (lens, cornea, retina, iris, and ciliary body) has revealed that qualitatively most of the fatty acid present is bound as "essential lipid." Consequently, the wide quantitative differences in lipid content of the several tissues implies a marked range in metabolic activity. The vitreous humor and the lens appear to be relatively inert in this respect.

REFERENCES

1. Wootton, J. F.; Young, R. G., and Williams, H. H.: Biochemistry of the Eye: I. Chromatographic Investigation of the Free Amino Acids of the Vitreous Humor. A. M. A. Arch. Ophth., this issue, p. 589.

2. Young, R. G., and Williams, H. H.: Biochemistry of the Eye: II. Gelatinous Protein of the Vitreous Body, A. M. A. Arch. Ophth., this issue, p. 593.

3. Sullmann, H.: Chemie des Auges, Tabulae biologicea, 1951, Vol. 22, Pt. 2.

4. Bloor, W. R.: A Colorimetric Procedure for the Determination of Small Amounts of Fatty Acid, J. Biol. Chem. **170**:671, 1947.

5. Sumner, J. B.: A Method for the Colorimetric Determination of Phosphorus, Science **100**:413, 1944.

6. Glick, D.: Concerning the Reineckate Method for the Determination of Choline, J. Biol. Chem. **156**:643, 1944.

7. Sperry, W. M., and Webb, M.: A Revision of the Schoenheimer-Sperry Method for Cholesterol Determination, J. Biol. Chem. **187**:97, 1950.

8. Kancher, M.; Galbraith, H.; Button, V., and Williams, H. H.: The Distribution of Lipids in Animal Tissues, Arch. Biochem. **3**:203, 1943.

9. Bloor, W. R.; Okey, R., and Corner, G. W.: The Relation of the Lipids to Physiological Activity: I. The Changes in the Lipid Content of the Corpus Luteum of the Sow, J. Biol. Chem. **86**:291, 1930.

GLYCOLYTIC ACTIVITY OF CILIARY PROCESSES

ANDREW de ROETTH Jr., M.D.
With the Technical Assistance of Mildred Orchen, B.A.
NEW YORK

IN A PREVIOUS communication,[1] the respiration of the ciliary processes was investigated, and it was found that a certain similarity exists between the metabolism of the ciliary processes and that of typical secretory glands, such as salivary glands. This was especially true in regard to the so-called "stimulation metabolism," i. e., the respiratory activity following stimulation of the excised surviving tissue slice with certain parasympathetic drugs, such as acetylcholine and physostigmine. Therefore, it was thought of interest to examine also the glycolytic activity of the ciliary processes, since it is known * that the "stimulation metabolism" affects also the glycolysis of the typical secretory glands. As a preliminary to this study it was necessary to investigate the various factors that influence the glycolytic activity of the ciliary processes. There are only a few scattered reports in the literature concerning glycolysis of the ciliary processes. The most recent one is that of Brückner,[5] who has only one or two observations concerning the anaerobic glycolysis of the ciliary processes. In the present study, therefore, an attempt was made first to establish the various factors influencing the glycolytic activity of the ciliary processes and then, in particular, to examine the glycolysis in regard to the so-called "stimulation metabolism," comparing it with the glycolytic activity found in typical secretory glands.

EXPERIMENTAL STUDY

In this investigation ciliary processes from 600 beef eyes were used, the eyes being obtained from freshly slaughtered animals. The ciliary processes were dissected according to the method of Friedenwald [6] and handled in the same manner as described in the previous communication. The anaerobic glycolysis in this investigation means the accumulation of lactic acid under anaerobic conditions; aerobic glycolysis will refer to the accumulation of lactic acid under aerobic conditions. For the anaerobic glycolysis the flasks were gassed with 95% nitrogen and 5% CO_2, and for the aerobic glycolysis a mixture of 95% oxygen and 5% CO_2 was employed. In most instances the glycolytic activity was determined with the Warburg manometric technique, employing the same type of flat-bottom Warburg flasks as described previously. Temperature, unless otherwise designated, was 37 C. For each reaction vessel anywhere from a quarter to a whole ciliary body was used. The total fluid volume in each flask was 3 ml., and the suspension medium in most instances was a balanced salt solution, designated as Kreb's I and consisting of the following: 80 parts of a 0.9% sodium chloride solution, 4 parts of 1.15% potassium chloride solution, 3 parts of 0.11 M calcium chloride solution, 1 part of 2.11% potassium biphosphate (potassium acid phosphate) solution, 1 part of 3.82% magnesium sulfate solution, and 21 parts of 1.3% sodium bicarbonate solution, pH 7.4. The suspension fluid was made up fresh for each day's determination and before use was gassed for 10 minutes with either the anaerobic or the aerobic gas mixture.

Since the conventional Warburg manometric technique measures only the evolution of carbon dioxide and presupposes that the acid produced is lactic acid, it was thought advisable to check

This study was supported by the Sloan Glaucoma Fund.

From the Institute of Ophthalmology of the Presbyterian Hospital.

* References 2, 3, and 4.

the results also with the direct determinations of lactic acid. This was done with the Barker-Summerson [7] method, which is a colorimetric method and is specific for lactic acid. Two flasks containing either quarters or halves of each of two ciliary processes were used. In the first flask the initial amount of lactic acid was determined after equilibration, and in the second flask the final amount of lactic acid was obtained at the end of the experiment, thus enabling the calculation of the amount of acid accumulated over the experimental period. Every alternate manometric experiment was checked with the direct chemical determination, but since the agreement between the chemical and the manometric determinations was within 15%, only the manometric determinations are reported in the results. The effect of pH changes was investigated by varying the pH of the suspension fluid. This was accomplished by changing the amount of sodium bicarbonate in the Kreb's I solution but maintaining the same gas mixture as described by Umbreit and associates [8] and Krebs.[9] In another series of experiments the pooled ciliary processes obtained from several beef eyes were homogenized in Kreb's I solution and then pipetted directly into the Warburg flasks. In one experiment the temperature employed was 27 C., instead of the conventional 37 C.

Various sugars and other metabolites, such as galactose 100 mg. per 100 cc. mannose 100 mg. per 100 cc. sorbose 100 mg. per 100 cc., mannitol 100 mg. per 100 cc., Na succinate 10^{-3}M, Na fumarate 10^{-3}M, Na pyruvate 10^{-3}M, Na glutamate 10^{-3}M, and Na malonate 10^{-3}M, were added to the suspension fluid.

TABLE 1.—*Anaerobic Glycolysis of Ciliary Processes of Beef Eyes, Expressed in Terms of Microliters of CO_2 Produced per Milligram Dry Weight Tissue per Hour, Each Figure Representing One Beef Eye*

	Suspension Fluids*			
	NaCl, 0.9%	NaCl + KCl 0.154 M 0.9%	Ringer's Solution	Kreb's I Solution
	7.7	7.1	7.1	9.9
	7.9	9.0	7.8	10.5
	8.2	7.9	7.9	9.0
	6.4	7.7	9.2	9.3
	7.5	8.1	8.4	8.6
Average	7.5	8.0	8.1	9.5
Standard deviation	± 0.307	± 0.215	± 1.10	± 1.06

* The suspension fluids contained, besides the substances indicated, 100 mg. glucose per 100 cc. and sufficient Na HCO_3 to maintain the pH at 7.4, as described by Umbreit and associates.[8]

In the experiment with acetylcholine chloride (0.066 mg. per 100 cc.) and physostigmine salicylate (4 mg. per 100 cc.), the physostigmine was added to the main compartment of the flask together with the suspension fluid and the tissue; the acetylcholine was placed in the side-arm of the Warburg flask and then tipped in at zero time at the beginning of the experiment. When the effect of iodoacetate (0.001 M), glyceraldehyde (0.005 M), and fluoride (0.01 M) was studied, the flasks with the sodium fluoride and their controls had no calcium chloride in the suspension fluid because the calcium chloride precipitated under these conditions. The tissue was weighed initially on a torsion balance, and 18% of this weight was estimated to be dry weight, as previously described. All results are expressed in terms of this dry weight measurement, $Q_{CO_2}^{N_2}$ measuring microliters of CO_2 accumulated per milligram of dry weight tissue per hour under anaerobic conditions (anaerobic glycolysis), and $Q_{CO_2}^{O_2}$ signifying microliters of CO_2 accumulated per milligram of dry weight tissue per hour under aerobic conditions (aerobic glycosis). The readings on the manometers were carried out over a period of one to two hours, but since the activity-time curve falls off noticeably after the first hour, the results were calculated for the first hour of each experiment only.

RESULTS

A. Anaerobic Glycolysis.—Table 1 shows that there was not much difference in the rate of anaerobic glycolysis of ciliary body when sodium chloride, sodium chloride plus potassium chloride, Ringer's solution, or Kreb's I solution was used as the suspension fluid, together with 100 mg. per 100 cc. of glucose and enough

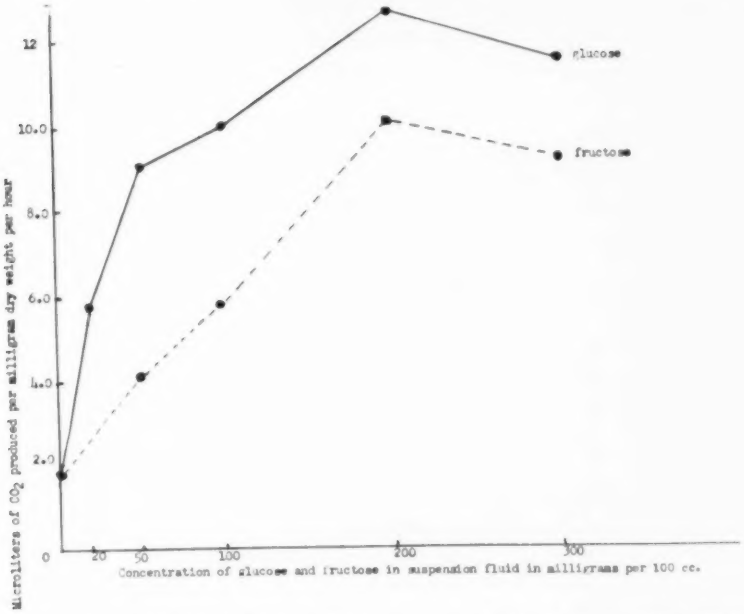

glucose
fructose
Microliters of CO_2 produced per milligram dry weight per hour
Concentration of glucose and fructose in suspension fluid in milligrams per 100 cc.

Chart 1.—Anaerobic glycolysis of ciliary processes at various concentrations of glucose and fructose, each curve representing the average values for 40 determinations on 20 beef eyes.

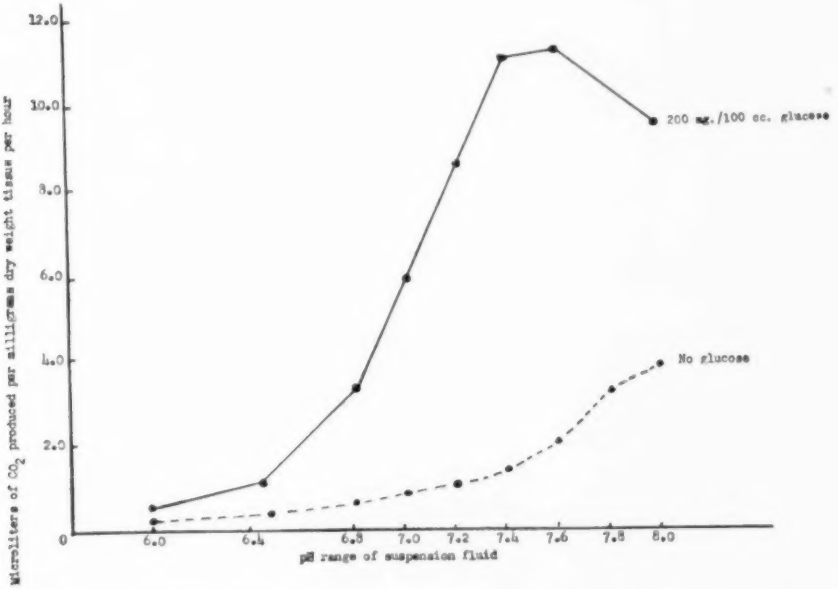

200 mg./100 cc. glucose
No glucose
Microliters of CO_2 produced per milligram dry weight tissue per hour
pH range of suspension fluid

Chart 2.—Anaerobic glycolysis of ciliary processes both in the presence and in the absence of added glucose, each line representing the average values of 50 determinations on 50 beef eyes.

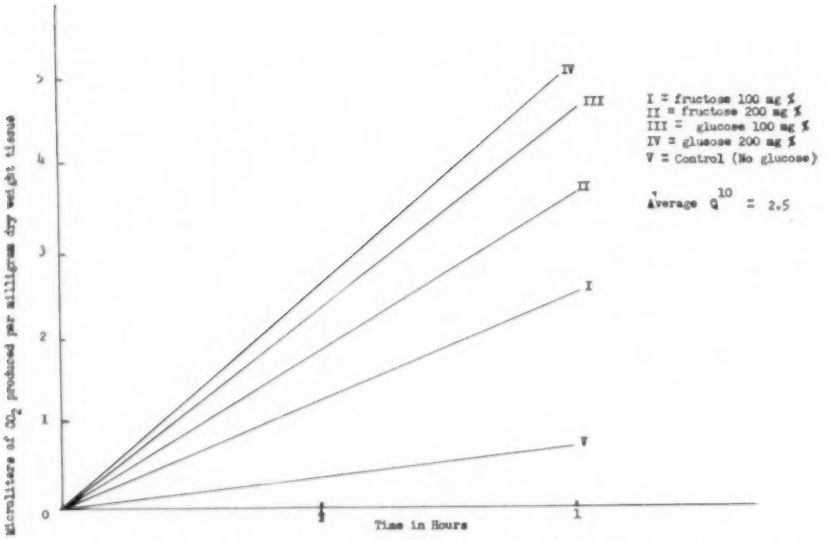


Chart 3.—Anaerobic glycolysis of ciliary processes at 27 C. (Q^{10} Experiment). Each line represents the average values of 10 determinations on 10 beef eyes. For temperature coefficient Q^{10} determinations compare above results with those at 37 C. as illustrated in Chart 1.

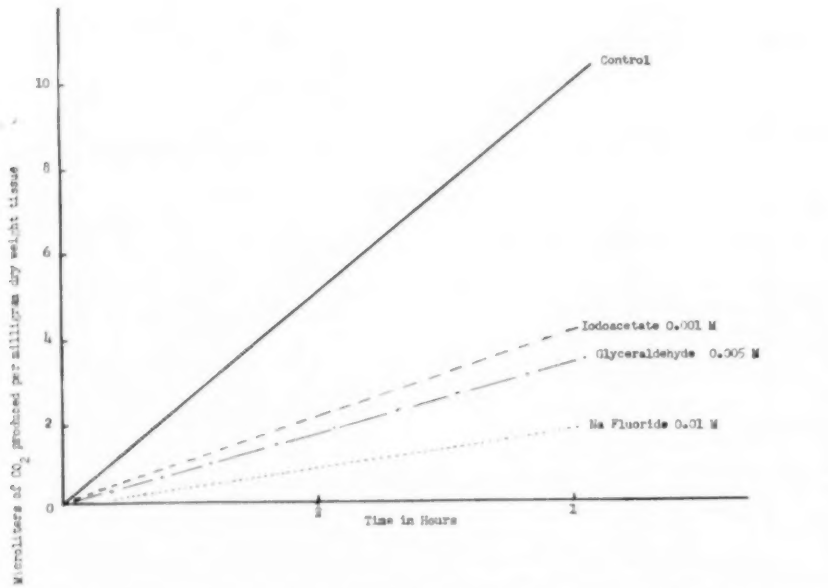


Chart 4.—Anaerobic glycolysis of ciliary processes in the presence of 100 mg. of glucose per 100 cc. showing inhibitory effect of iodoacetate (0.001 M final concentration), glyceraldehyde (0.005 M) and Na fluoride (0.01 M final concentration); each line represents the average value of 20 determinations on 10 beef eyes.

bicarbonate to maintain the pH constant at 7.4. However, it is noticed that the Kreb's I solution showed the highest glycolytic activity, 9.5 $Q_{CO_2}{}^{N}$ units. Therefore, for all subsequent experiments this was used as the suspension fluid.

In Chart 1 the effects of various concentrations of glucose and fructose were determined, and it was found that even without any added sugar the ciliary processes did show a minimal amount of anaerobic lactic acid production (1.7 $Q_{CO_2}{}^{N}$). Furthermore, even small amounts of glucose or fructose, such as 20 or 50 mg. per 100 cc., showed a marked increase in the glycolytic activity rates. The highest rate of anaerobic lactic acid accumulation occurred in the presence of 200 mg. per 100 cc. fructose or glucose, the values being 10.1 and 12.5 $Q_{CO_2}{}^{N}$ units, respectively. Increasing the concentration of the sugars above this level did not cause a further increase in glycolysis.

Chart 2 demonstrates the effect of variation in the pH of the suspension medium; both in the presence and in the absence of glucose, increasing the pH from the acid toward the alkaline side caused a corresponding increase in the glycolytic

TABLE 2.—*Aerobic Glycolysis of Ciliary Processes, Expressed in Terms of $Q_{CO_2}{}^{O_2}$ Units, Microliters of CO_2 Produced per Milligram Dry Weight Tissue per Hour (Indirect, Manometric Method) and $Q_L{}^{O_2}$ Units, Micrograms of Lactic Acid Accumulated per Milligram Dry Weight Tissue per Hour (Direct Chemical Determinations)***

	Control		Acetylcholine + Physostigmine	
	$Q_{CO_2}^{O_2}$	$Q_L^{O_2}$	$Q_{CO_2}^{O_2}$	$Q_L^{O_2}$
Experiment 1	1.32	7.0	1.59	6.0
Experiment 2	1.20	6.2	0.98	8.0
Experiment 3	0.93	6.0	1.40	4.0
Experiment 4	1.49	7.4	1.54	8.4
Experiment 5	1.28	4.0	1.28	6.6
Experiment 6	1.46	5.3	1.36	4.0

* Final concentration of physostigmine was 4 mg. per 100 cc. and that of acetylcholine 0.006 mg. per 100 cc. Since 1 μ L of CO_2 is equivalent to 4 γ of lactic acid, the results show fairly close agreement of the indirect manometric with the direct chemical determinations. Four beef eyes were utilized for each experiment, one quarter from each of the four eyes being placed in every Warburg flask.

activity of the tissue. The maximum activity was noticed at pH 7.4 to 7.6, i. e., in the range of the pH extracellular body fluids.

The anaerobic glycolytic activity of the ciliary processes at 27 C. is seen in Chart 3. A comparison with Chart 1 shows that the glycolytic activity rate at 27 C. was less than half that found at 37 C., the temperature coefficient (Q^{10}) being about 2.5 in this temperature range.

Chart 4 shows that iodoacetate, glyceraldehyde, and sodium fluoride in small concentrations markedly inhibited the glycolytic activity of the ciliary process, the amounts of inhibition being 67%, 73%, and 85%, respectively.

B. Aerobic Glycolysis.—Control experiments showed that lactic acid did not accumulate in this tissue under aerobic conditions in the absence of glucose or fructose. Therefore in all the subsequent experiments 100 mg. per 100 cc. of glucose was employed in the suspending medium, the average $Q_{CO_2}{}^{O_2}$ units being 1.3.

Table 2 indicates that acetylcholine and physostigmine had no effect on the aerobic glycolysis of the ciliary processes; since this was a crucial experiment, the results of both the manometric and the direct chemical determinations are reported here.

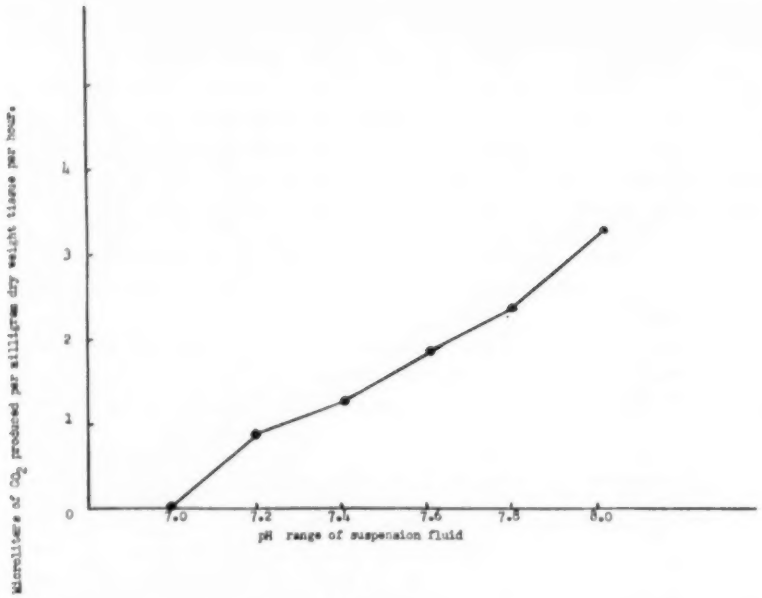


Chart 5.—Aerobic glycolysis of ciliary processes, showing effect of change in pH of the suspension fluid. Each circle represents the average of 10 determinations on 10 beef eyes. Below pH of 7.0 there was no noticeable lactic acid accumulation.

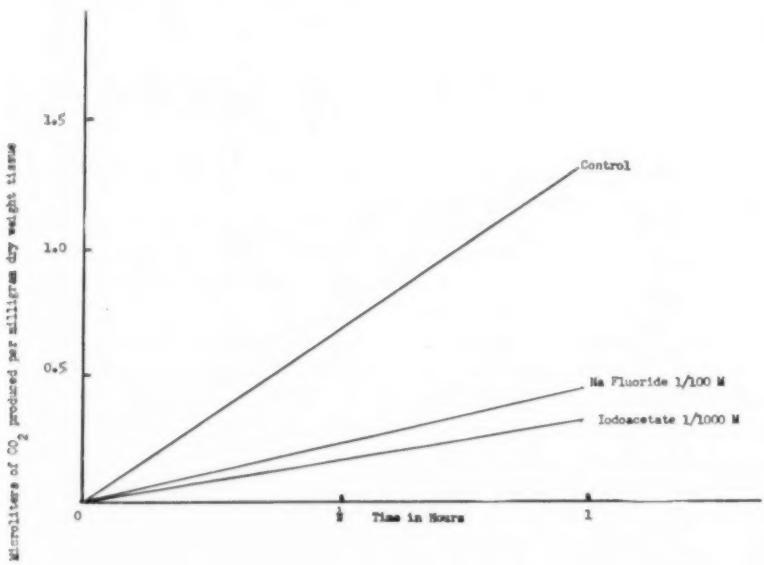


Chart 6.—Aerobic glycolysis of ciliary processes showing inhibitory effect of iodoacetate (0.001 M final concentration) and Na fluoride (0.01 M final concentration); each line represents the average value of 20 determinations on 20 beef eyes.

In Chart 5 is demonstrated the effect of pH variation on the aerobic glycolytic activity, showing a gradual increase in the rate of lactic acid accumulation between pH 7.0 and 8.0.

Chart 6 illustrates the inhibitory effect of small amounts of iodoacetate and fluoride on the aerobic lactic acid production of the ciliary processes, the amount of inhibition being 75% and 65%, respectively.

Galactose, mannose, sorbose, mannitol, Na succinate, Na fumarate, Na pyruvate, Na glutamate, and Na malonate had no effect on either the anaerobic or the aerobic lactic acid accumulation in this tissue.

The homogenized ciliary processes showed reduced glycolytic activity rates, the values being about one-tenth those of the undisturbed tissue. This illustrates the effect of damage, such as homogenation, on the metabolic activity of isolated, surviving tissues.

COMMENT

As a preliminary experiment, it was of importance to determine what suspension fluid should be employed for glycolytic activity studies on this tissue. Table 1 demonstrates that there is very little difference in sodium chloride, Ringer's solution, sodium chloride plus potassium chloride, and Kreb's I solution in regard to the glycolytic activity rates as long as the pH is controlled; as can be seen from this Table, all the suspension fluids contained identical amounts of bicarbonate, thus maintaining the pH at 7.4. However, because in Kreb's I solution the glycolytic activity rates were slightly higher than in the other salt solutions, this solution was used as the suspension fluid in all subsequent experiments. Various reports on glycolytic activities of other tissues show that a balanced salt solution resembling that of the Kreb's I solution is probably the optimum medium for such metabolic investigations. The previous communication demonstrated that also for the respiratory activity a balanced salt solution was the optimum suspension fluid.

Various sugars and other metabolites, such as galactose, mannose, sorbose, mannitol, succinate, fumarate, pyruvate, glutamate, and malonate, were added to the Kreb's I solution, but only glucose and fructose were noticed to have any effect on either the anaerobic or the aerobic glycolytic activity of the ciliary processes. As can be seen in Chart 1, even small amounts of the two sugars were sufficient to increase considerably the glycolytic activity of the ciliary processes. Also, it can be noticed that glucose increased the glycolytic activity somewhat more than fructose. If we compare this with the activity of other secretory glands, e. g., the salivary gland,† we note that the anaerobic glycolysis of the latter is increased considerably with the addition of glucose. Fructose, however, has very little, if any, effect on the anaerobic glycolysis of the salivary gland.

The variation of the glycolytic activity with the pH range both under anaerobic and under aerobic conditions resembles that of many other tissues showing an increased lactic acid accumulation with an increase in pH. Below a pH of 6 there was very little, if any, glycolytic activity; this activity increased rapidly up to about pH of 7.6, at which it was maximum. At a pH of 8 the glycolytic activity appeared to decrease again. Thus, it seems that in the presence of added glucose, the optimum glycolytic activity is in the range of the physiological pH of the so-called extracellular fluids; this characteristic is demonstrated by many other tissues. If we

† References *2* and *3*.

compare the experiment at 37 C. with that at 27 C., it can be noted that at 27 C. the glycolytic activity of the ciliary body in the presence both of fructose and of glucose is less than half that at 37 C. The calculated Q^{10}, i. e., the temperature coefficient, is on the average 2.5 between these two temperatures, signifying a two-and-a-half-fold increase in anaerobic glycolysis; in this respect the ciliary processes resemble other mammalian tissues.

Iodoacetate and fluoride depressed both the anaerobic and the aerobic glycolysis of this tissue considerably. Since it is known that iodoacetate inhibits the activity of phosphoglyceraldehyde dehydrogenase and fluoride inhibits mainly the action of enolase, the above experiments suggest the presence of these enzymes in the ciliary process. Glyceraldehyde in small concentrations considerably inhibited the anerobic lactic acid production of this tissue, indicating that the glycolysis of the ciliary processes is mainly glucose glycolysis, and not glycogen glycolysis.

It has been demonstrated [10] that the inhibition of anaerobic glycolysis in a tissue parallels the magnitude of glycolysis of the tissue. In this respect the ciliary processes demonstrate very high glycolytic rates, since their glycolysis was inhibited markedly by small amounts of fluoride and iodoacetate. The highest glycolytic activity obtained in the anaerobic experiments were in the region of 12 $Q_{CO_2}{}^{N}$ units, placing the ciliary processes in a category of actively metabolizing tissues. However, if we take into consideration the architecture of the ciliary processes, we realize that the anaerobic glycolysis of the active part of this tissue, namely, the ciliary epithelium, is probably considerably higher than the above value, for the following reason: The dissected ciliary processes contain, besides the ciliary epithelium, large amounts of underlying connective tissue stroma. Even with the most careful method of dissection there still is a considerable amount of stroma which remains with the ciliary epithelium in this dissection process. It is estimated that the dissected ciliary process strips from the beef ciliary bodies contain about half ciliary epithelium and half underlying connective tissue stroma by weight. It is generally recognized that connective tissue shows limited metabolic activity, including low rates of glycolysis; therefore, it might be assumed that most of the glycolytic activity of the ciliary processes is due to the epithelial layer itself. Since the ciliary epithelium represents only about half the weight of the total tissue strip, the glycolytic activity rate of the ciliary epithelium itself is probably considerably more than the 12 $Q_{CO_2}{}^{N_2}$ units indicated above. It might be estimated to be somewhere in the neighborhood of 20 $Q_{CO_2}{}^{N_2}$ units. Brückner [5] reports a glycolytic activity of 19 $Q_{CO_2}{}^{N_2}$ units for the ciliary processes of beef eyes; and, although he employed a slightly different method of dissection than that followed in this study, the present results are of the same order of magnitude as Brückner's previous finding. Embryologically the ciliary epithelium is analogous to the neuroepithelium of the retina. It is well known that from the biochemical point of view the retina has one of the highest metabolic activities of all mammalian tissues studied so far; it has a very high oxygen uptake and also a very high glycolytic activity. Therefore, one might suppose that the ciliary epithelium would show comparable high metabolic activity. The present investigation indicates that at least as far as the anaerobic glycolytic activity is concerned the ciliary epithelium tends to approximate that of the retina.

The previous communication showed that respiratory activity was considerably lowered by homogenizing the ciliary processes. The present investigation demon-

strates that the glycolytic rates—both in the anaerobic and in the aerobic experiments—were also markedly influenced by homogenizing the tissue. Thus, the optimum metabolic activity seems to depend on the structural integrity of the tissue; and since the dissected ciliary process is in itself an ideally arranged tissue slice, it lends itself conveniently to metabolic studies. Any injury to this tissue, such as macerating or homogenizing, would further decrease its metabolic activity and therefore interfere with our investigation.

At the 1939 Cold Spring Harbor Symposium, Burk [11] discussed the Meyerhof quotient, which is the anaerobic glycolysis minus the aerobic glycolysis divided by the respiratory activity of the tissue, $\frac{Q_{CO_2}{}^{N_2} - Q_{CO_2}{}^{O_2}}{Q_{O_2}}$. In most tissues this commonly varies from 1 to 2, but it is considerably higher in actively metabolizing tissues. In the ciliary processes the Meyerhof quotient was calculated to be approximately 3, the equation being $\frac{12 - 1.4}{3.6} = 3.0$. This, again, would place the ciliary processes in a group of very actively metabolizing tissues.

The most significant result of the aerobic experiments is seen in Table 2, according to which the effect of acetylcholine and physostigmine on the aerobic glycolysis of the ciliary processes was negligible. This negative result is of interest, because Deutsch and Raper [3] a number of years ago demonstrated that in typical secretory glands, such as the salivary gland, parasympathomimetic drugs caused an increased amount of aerobic lactic acid accumulation. This was particularly the case with acetylcholine and physostigmine. The result of this experiment therefore would indicate that as far as the aerobic glycolysis is concerned, the ciliary body does not behave in the same way as the typical secretory glands; i. e., it does not show the typical "stimulation metabolism." The previous communication, however, demonstrated that as far as the oxygen uptake of this tissue was concerned, it did show the "stimulation metabolism" following the addition of acetylcholine and physostigmine. Thus it would seem that from the biochemical point of view the ciliary processes, although in some respects resembling secretory glands, do not demonstrate all the typical metabolic patterns of other known secretory glands. This biochemical information might be related to other characteristics of this tissue, since it is known that from a physiological or clinical point of view the ciliary processes are not typical of other known secretory glands.

SUMMARY

The anaerobic lactic acid production of the dissected ciliary processes of beef eyes showed a very high activity. For optimum glycolytic activity a balanced, buffered salt solution with a pH of approximately 7.4 to 7.6 was found to be optimal. This glycolytic activity was markedly inhibited by sodium fluoride, glyceraldehyde, and iodoacetate. The temperature coefficient of the anaerobic glycolytic activity of the ciliary processes was found to be in the neighborhood of 2.5. Acetylcholine and physostigmine did not influence the aerobic lactic acid accumulation in the ciliary processes. It was estimated that the anaerobic glycolytic activity of the ciliary epithelium is in the same order of magnitude as that of the retina, thus placing it among the most active of mammalian tissues. The Meyerhof quotient was calculated to be 3.0 for the ciliary epithelium, which would again indicate it to be a very actively metabolizing tissue.

It was concluded that from the biochemical point of view the ciliary processes resemble, but are not typical of, other known secretory glands.

635 West 165th St. (32).

REFERENCES

1. de Roetth, A., Jr.: Respiration of Ciliary Processes, A. M. A. Arch. Ophth. **50**:491, 1953.

2. Brock, N.; Druckrey, H., and Harken, H.: Untersuchungen über Glycolyse, Biochem. J. **300**:1, 1938.

3. Deutsch, W., and Raper, H. S.: Respiration and Functional Activity, J. Physiol. **87**:275, 1936.

4. Deutsch, W., and Raper, H. S.: The Respiration and Metabolism of Submaxillary Gland Tissue of the Cat, J. Physiol. **92**:439, 1938.

5. Brückner, R.: Über Atmung und anaerobe Glykolyse in Geweben der Rinderuvea, Ophthalmologia **109**:19, 1945.

6. Herrmann, H., and Friedenwald, J. S.: The Choline Esterase Content of the Choroid Plexus and Ciliary Processes, Bull. John Hopkins Hosp. **70**:14, 1942.

7. Barker, S. B., and Summerson, W. H.: Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535, 1941.

8. Umbreit, W. W.; Burris, R. H., and Stauffer, J. F.: Manometric Techniques and Tissue Metabolism, Minneapolis, Burgess Publishing Company, 1949.

9. Krebs, H. A.: Body Size and Tissue Respiration, Acta biochim. et biophys. **4**:249, 1950.

10. Dickens, F., and Grenille, G. D.: Anaerobic Conversion of Fructose into Lactic Acid by Tumour and Adult Normal Tissue, Biochem. J. **26**:1546, 1932.

11. Burk, D.: A Colloquial Consideration of the Pasteur and Neo-Pasteur Effects, Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, N. Y., 1939, Vol. 7, p. 420.

A MODIFIED KRÖNLEIN OPERATION

RAYNOLD N. BERKE, M.D.
HACKENSACK, N. J.

AN INGENIOUS operation for resection of the lateral wall of the orbit for the removal of orbital dermoids was described by Krönlein in 1888.[1] For many years this was the method of choice for the treatment of retrobulbar tumors, but of late years it has fallen into disuse in many places for several reasons: (1) The procedure as done with the Gigli saw was technically not easy; (2) an unsightly scar sometimes resulted (Fig. 1); (3) adequate working space often was lacking (Fig. 2), and (4) other procedures * completely replaced the Krönlein operation in some places.

The purpose of this article is to present a simplified Krönlein operation which is relatively easy, will give greater exposure, will leave an inconspicuous scar, and, of itself, can do no damage to the orbital or periorbital structures.

ANATOMY OF LATERAL WALL OF THE ORBIT

Fortunately, the lateral wall is so constructed that its resection is relatively simple with the proper equipment. A glance at Figure 3 shows that this wall may be divided into four parts according to its thickness, the anterior part being thick along the orbital margin, the second portion being very thin, the third portion thick, and the fourth, or intracranial, part thin. The fact that the second part is thin makes it easy to break the bone at this point; the thickness of the third part makes it impossible to enter the cranial cavity unintentionally.

In the procedure to be described, the thick anterior part of the lateral wall is cut above and below (Figs. 4 and 5) with a Stryker oscillating saw for a distance of 10 to 12 mm., after which the second, or thin, part of the lateral wall is fractured by means of a heavy forceps and the bone flap retracted laterally. Figure 6 illustrates the amount of exposure achieved after resecting a moderate amount of the lateral wall. The thick dark line in Figure 5 represents the junction of the lateral cranial wall with the lateral orbital wall. Behind this line lies the temporal fossa of the cranial cavity.

Figure 7 illustrates the relative sites for the bone cuts for the classic Krönlein operation (*XYZ*) and for the modified technique (*ABCD*) sponsored here. The

Read at the Eighty-Ninth Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., May 28-30, 1953.

* The Benedict [2] approach through the periosteum along the superior orbital margin, the Davis [3] approach through the skin of the lower lid, the Reese [4] approach through an external canthotomy, the nasal approach through the skin or conjunctiva,[5] and the transcranial approach as endorsed by Dandy [6] and Naffziger.[7]

zigzag line, *BC*, represents the site of fracture of the bone in the latter technique. The bone between the inferior orbital fissure and the line *BC* is sometimes ronguered away to give added exposure. Thus, it is obvious that this new technique gives considerably more working space for removing an retrobulbar tumor than is achieved by the classic procedure.

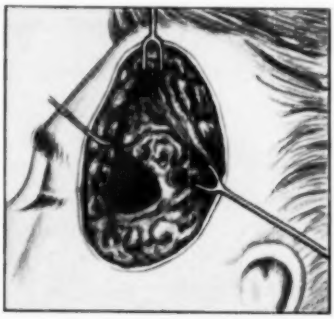


Fig. 1 (left).—Unsightly scar which sometimes results from the classical Krönlein operation. From Foster.[17]

Fig. 2 (right).—Amount of exposure procured by the classical Krönlein operation. Drawing by Krönlein.[1]

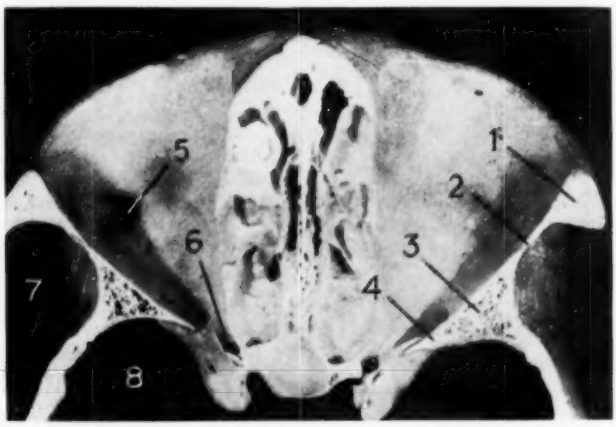


Fig. 3.—Horizontal section through orbits.

1, anterior thick part of lateral orbital wall; *2*, anterior thin part of lateral orbital wall adjacent to temporal fossa (*7*); *3*, posterior thick part of lateral orbital wall, formed by junction of this wall with lateral wall of the middle cranial fossa; *4*, posterior thin part of lateral orbital wall, showing orbital cavity in front and cranial cavity behind; *5*, dehiscence in roof of right orbit; *6*, roof of right optic canal; *7*, temporal fossa (contains temporal muscle in life); *8*, middle fossa of cranial cavity (contains temporal lobe of brain in life).

Lateral to the second part of the lateral wall is the temporal fossa (Figs. 3 and 9), which in life is occupied by the temporal muscle—a muscle of mastication, which is easily retracted out of the way during the operation and which tolerates this surgical trauma exceedingly well. The relationship of the retrobulbar tissues to the frontal lobe of the brain, to the nasal cavity, to the antrum, and to the temporal muscle is

illustrated in Figure 9. Note the thin layer of bone between the lateral rectus muscle and the temporal muscle. This bone is easily rongeured away to gain added exposure should this be necessary. Most orbital tumors are found above, below, or lateral to the optic nerve, only 2 of the 25 tumors in this series being on the nasal side.

Thus, the lateral wall is ideally suited for orbitotomy, because (1) no important periorbital tissue is endangered by the operation, (2) because it is the most accessible and easiest portion of all the orbital walls to resect, and (3) because resection of 1 sq. in. (6.5 sq. cm.) of the lateral wall gives considerably greater exposure of the retrobulbar space than can a similar amount of resection of any of the other walls.

After the lateral wall has been resected, the retrobulbar space is exposed to view. The muscles, nerves, and blood vessels are not usually visualized, however, because these structures are occluded by much loose areolar tissue and orbital fat. Nevertheless, the globe, the optic nerve, and the extraocular muscles are readily identified by palpation. To visualize these important and delicate structures, most of which lie lateral to the optic nerve (Fig. 8), one must gently retract the orbital fat. By this means, the extraocular muscles, the optic nerve, the superior ophthalmic vein, the ophthalmic artery, the lacrimal artery, the nerve to the inferior oblique muscle, and even the ciliary ganglion, may be visualized. However, it is rarely necessary to visualize all these structures in removing a retrobulbar tumor.

TECHNIQUE

A good overhead light that will focus a concentrated beam into the orbit is essential to visualize properly the retrobulbar tissues. A second assistant is generally needed to retract the bone flap and the adjacent tissues. The following instruments are useful:

1. One Stryker bone saw (Fig. 10)
2. One Bard-Parker knife with handle, No. 3
3. One Mayo scissors
4. One Stevens scissors
5. One Ewald forceps
6. Two muscle hooks
7. Two Desmarres lid retractors
8. Two double-ended retractors
9. Two blunt rake retractors
10. Malleable retractors, three sizes
11. Six Alles clamps
12. Two rongeurs, two sizes
13. Twelve mosquito hemostats
14. One chisel and mallet
15. One suction tip with tubing
16. One suture scissors
17. One needle holder
18. Two fixation forceps (no catch)
19. Two Lester forceps (one heavy)
20. Sutures:

    One 3-0 nonabsorbable surgical (silk) for suturing lid margins together
    One 3-0 silk for placing under external rectus muscle
    One 3-0 silk for marking external canthal ligament
    One 4-0 chromic absorbable surgical (gut) suture for closing periosteum
    One 4-0 plain surgical gut for tying vessels
    One 4-0 plain surgical gut for subcutaneous tissues
    One 6-0 silk for closing skin

21. One roll of 2-in. (5-cm.) gauze for pressure dressing
22. Four towel clips for draping patient

With the patient under general anesthesia, the skin of the brow, lids, and temple is prepared with tincture of iodine and alcohol or some other suitable skin antiseptic. The patient's head is

cradled in sandbags with the temple turned upward and the head rotated slightly to the opposite side. After draping the patient with sterile sheets or towels, the operation is begun. The steps of the operation are as follows:

1. One intermarginal suture is placed between the medial halves of the upper and lower lids to protect the cornea during and after the operation.†

Fig. 4.—Right orbit viewed from temporal side, illustrating position of upper and lower bone cuts through lateral orbital wall.

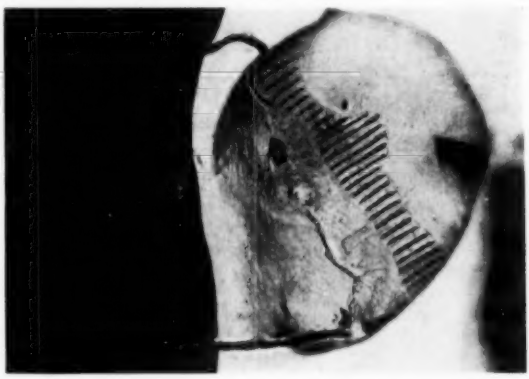


Fig. 5.—Right orbit viewed from nasal side, showing position of upper and lower bone cuts through lateral orbital wall.

The shaded area represents the line of fusion between the lateral orbital wall and the lateral cranial wall, posterior to which lies the middle fossa of the cranial cavity and the superior orbital fissure. The bone between the upper and lower bone cuts is easily broken and retracted laterally; then the remaining bone posterior to the break may be rongeured away as far as the shaded area without fear of entering the cranial cavity.

2. A long silk suture is inserted under the tendon of the lateral rectus muscle through the conjunctiva; the cornea is then rotated nasally under the medial one-half of the lids by hanging a small hemostat to the ends of the suture over the bridge of the nose.

3. The skin and subcutaneous tissues of the temple are incised with a scalpel for a distance of 30 to 40 mm. down to the temporal fascia from the external canthus toward the ear (Fig. 11).

† Omitted from the illustrations to simplify the artist's work.

The sharp bleeding which usually occurs is controlled with a few fine hemostats. Later these are removed to give better exposure. Occasionally a bleeding vessel may have to be tied off.‡

4. The external canthotomy is now extended through the conjunctiva to the lateral orbital margin with scissors, and the upper and then the lower skin flaps are lifted up with fixation forceps and the skin and subcutaneous tissues undermined from the temporal fascia for about 20 mm. in all directions (Fig. 12).

5. The upper and lower limbs of the external canthal ligament are now earmarked by means of sutures, and the ligament, together with the septum orbitale (but not including the con-

Fig. 6.—Front oblique view of right orbit after lateral orbital wall has been excised as far as shaded area in Figure 5.

Note that the optic foramen is visible in the apex of the orbit.

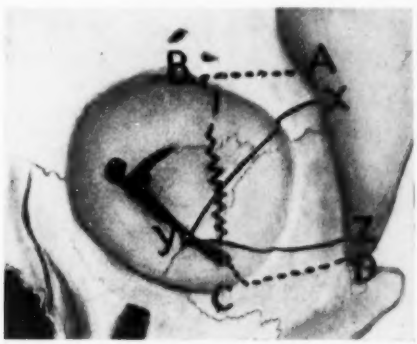


Fig. 7.—Front view of left orbit illustrating relative amounts of exposure obtained by classical Krönlein operation (*XYZ*) and modified procedure (*ABCD*). The zigzag line between *B* and *C* represents the site for breaking the lateral wall after the upper (*AB*) and lower (*CD*) bone cuts have been completed. Note that the area *ABCD* is considerably greater than the area *XYZ*. Modified from Wiener and Scheie.[38]

junctiva), is freed from the lateral orbital margin up to the superior and down to the inferior orbital margin (Fig. 13).

6. Te periosteum is now incised to mark the site of the bone cuts, the lower incision being made horizontally from the inferior orbital margin to just above the temporal process of the zygomatic bone and the upper from the superior orbital margin to the upper part of the temporal fossa about 10 to 12 mm. above the lateral orbital tubercle (Fig. 14).

‡ A similar incision was made by Swift [8] to expose the retrobulbar space in a patient with malignant exophthalmos, using a chisel and hammer to remove the lateral bony wall.

7. After a wide retractor is inserted between the globe and the periosteum above, the upper skin flap is retracted, and the lateral orbital margin is incised with the Stryker bone saw for a distance of 10 to 12 mm., care being taken to direct the blade at an angle of about 45 degrees toward the floor of the orbit (Figs. 6 and 15). Bleeding from the bone is controlled by suction.

8. The retractor is then inserted between the globe and the periosteum below, the lower skin flap retracted, and the lower bone cut made similarly, except that here the direction of the cut is roughly parallel with the floor of the orbit (Figs. 6 and 16).

9. The check ligament of the external rectus muscle is now severed with scissors and the lateral wall fractured by means of a heavy rongeur forceps and the bone flap turned laterally (Fig. 17),§ after which the sharp ridge of bone deep to the fracture is rongeured away to give more exposure if needed. Bone wax may be used to control the bleeding, but this is not usually necessary.

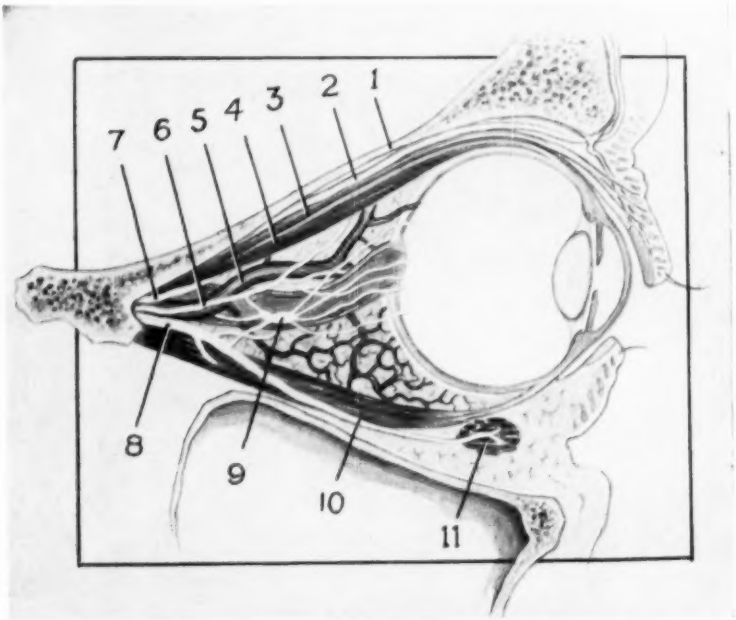


Fig. 8.—Sagittal section of right orbit.

1, roof of orbit; *2*, frontal nerve; *3*, levator muscle; *4*, superior rectus muscle; *5*, ophthalmic artery; *6*, nasociliary nerve; *7*, upper division of third cranial nerve; *8*, lower division of third cranial nerve; *9*, ciliary ganglion; *10*, nerve to inferior oblique muscle; *11*, inferior oblique muscle.

10. The retrobulbar tissues are now accessible for inspection by retracting the external rectus upward or downward (Fig. 18). If the tumor is not visible, the tissues should be gently palpated to locate the mass. A tumor large enough to cause exophthalmos may be located in any part of the retrobulbar area by palpation.

Once the tumor has been located, its removal may be very simple. If encapsulated, it may be removed by finger dissection alone without causing the slightest damage to the function of the eye. If, however, the tumor is attached to the retrobulbar tissues, blunt scissors dissection will usually be necessary. Under no circumstances should sharp dissection be used to excise the tumor without direct visualization and without first identifying the optic nerve and the external

§ In children and women this can often be done with the fingers; in very thick skulls a chisel and hammer may be needed to fracture the bone.

rectus muscle. The position of the external rectus can be noted by pulling on the suture already placed under the tendon while palpating for the muscle in the retrobulbar space. The optic nerve can be visualized by gently retracting the orbital fat (Fig. 18).

When the tumor is not encapsulated, but diffusely invades the retrobulbar tissues, one must expect considerable damage to the function of the eye if one elects to excise the tumor

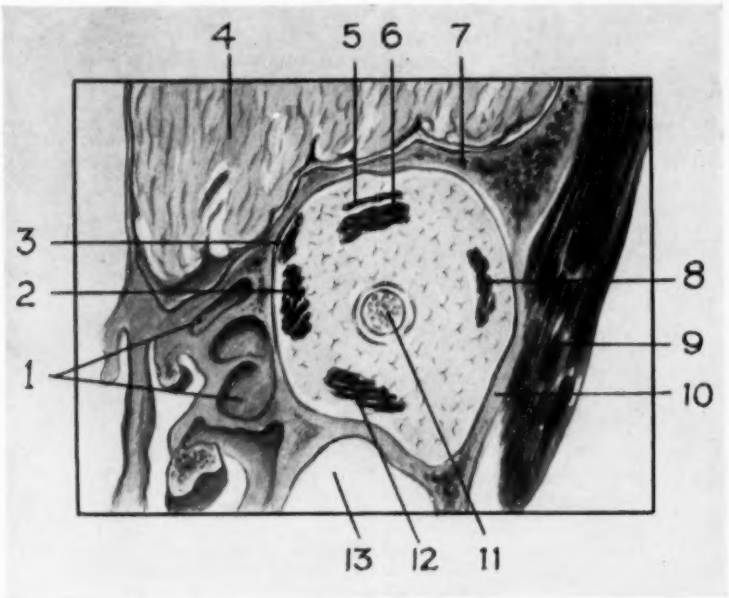


Fig. 9.—Frontal section through left orbit behind eyeball.

1, ethmoid sinuses; *2*, medial rectus muscle; *3*, superior oblique muscle; *4*, frontal lobe of brain; *5*, levator muscle; *6*, superior rectus muscle; *7*, roof of orbit; *8*, lateral rectus muscle; *9*, temporal muscle; *10*, lateral orbital wall; *11*, optic nerve; *12*, inferior rectus muscle; *13*, antrum.

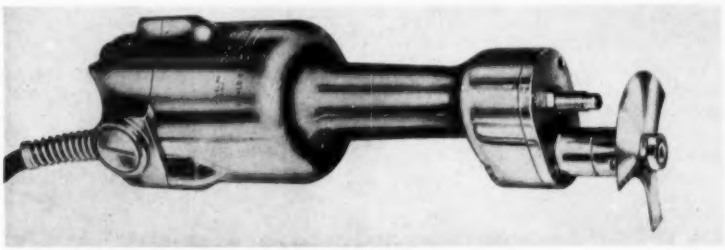


Fig. 10.—Stryker oscillating bone saw.

This instrument has greatly simplified the task of incising the bone for lateral orbitotomy because it does not cut soft tissues, requires less retraction of the tissues, and is safer for the operator and his assistants than the circular rotating saw.

in toto. Therefore, one should not attempt complete removal of such tumors *en masse* unless one is relatively certain that a malignant growth is present. Many of these diffuse tumors are pseudotumors (granulomas), which tend to regress spontaneously; some are diffuse hemangiomas, which may not continue to grow even if not completely excised; some are lymphosarcomas, which are amenable to x-radiation.

If a tumor is not readily located, the extraocular muscles should be examined to determine whether they are enlarged. When normal, these structures are not ordinarily visualized and are best identified by palpation—the external rectus by traction on the conjunctival suture, and the superior, medial, and inferior rectus muscles by palpation against the corresponding orbital wall.

11. After the tumor has been removed and the bleeding controlled, the bone flap is swung back into position and the periosteum along the bone cuts closed by means of two or three 0000 chromic absorbable surgical (gut) sutures. Because the periosteum is nonelastic, the cut edges cannot be closely approximated by sutures. Therefore, one should not be disturbed if a gap remains, because healing always occurs without complication (Fig. 19).

12. The upper and lower arms of the external canthal ligament are now picked up, the identifying sutures removed, and the ends of the ligament anchored to the periosteum adjacent to the lateral orbital tubercle by means of 0000 chromic absorbable surgical sutures. The con-

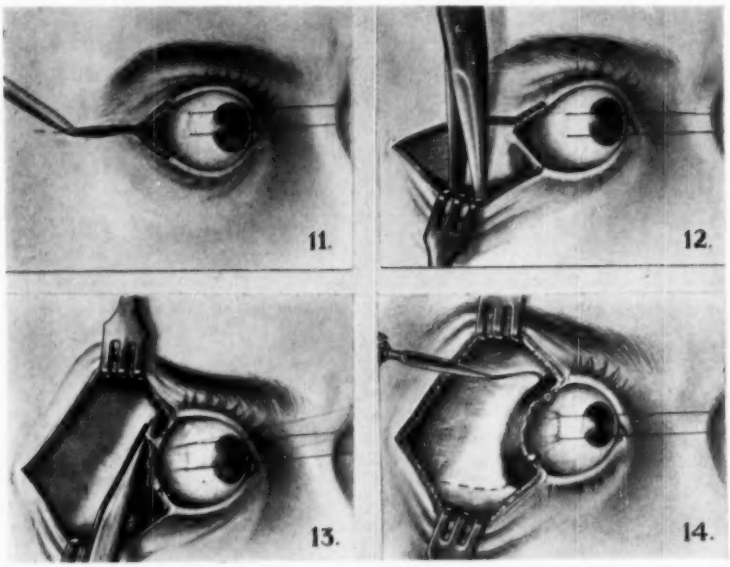


Fig. 11 (upper left).—Skin and subcutaneous tissues are incised laterally for a distance of 30 to 40 mm. to the temporal fascia covering the temporal muscle. The external canthotomy is best done with scissors.

Fig. 12 (upper right).—The lower skin flap is undermined with heavy scissors from the temporal fascia and the lateral orbital margin.

Fig. 13 (lower left).—After the upper and lower limbs of the external canthal ligament are tagged, this structure and the septum orbitale are cut free from the lateral orbital margin, care being taken not to incise also the lateral fornix.

Fig. 14 (lower right).—The periosteum of the lateral orbital wall is incised above and below parallel with the superior and inferior orbital margins to mark the site of the bone cuts. Note the position of the check ligament of the lateral rectus muscle midway between these incisions. Later this ligament is freed from the lateral wall.

junctival side of the external canthal ligament may be closed, if necessary, by plain absorbable surgical (gut) sutures.

13. The upper and lower skin flaps are carefully approximated by buried 0000 plain absorbable surgical sutures, after which the skin edges are brought together by several fine nonabsorbable surgical (silk) sutures. Special care should be taken to close accurately the skin edges lateral to the external canthus.

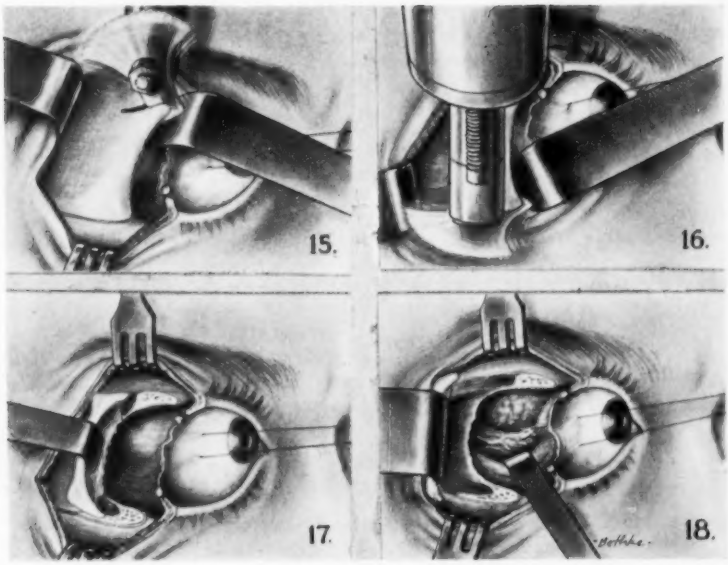


Fig. 15 (upper left).—The skin and the orbital contents are retracted away from the lateral bony wall above, and the bone is incised with the Stryker bone saw for a distance of 10 to 12 mm. at an angle of about 45 degrees to the floor of the orbit.

Fig. 16 (upper right).—The skin and the orbital contents are retracted away from the lateral orbital margin below, and the lower bone cut is made parrallel with the floor through the thick anterior part of the wall for a distance of 12 to 15 mm.

Fig. 17 (lower left).—After freeing the check ligament of the lateral rectus muscle, the lateral wall is broken with rongeur forceps and the incised section of bone retracted laterally. The ridge of bone posterior to the break may be rongeured away to gain added exposure if necessary.

Fig. 18 (lower right).—The retrobulbar contents are now accessible. By retraction of lateral rectus muscle and the orbital fat downward, a medium-sized tumor above the optic nerve is exposed to view.

Fig. 19.—X-ray of orbits after resection of left lateral wall to show position of excised bone.

14. A second intermarginal suture may be placed between the lids if desired, the wound edges smeared with an antibiotic ointment, and a roller gauze pressure dressing applied.

Postoperative Care.—The pressure dressing is left in place for four to five days, when the intermarginal sutures are removed. By the following day, if the skin wound is well healed, the silk sutures may be taken away. Usually there is marked edema of the lids for several days. If the external rectus muscle has been retracted under considerable tension during the operation, occasionally weakness of this muscle may persist for weeks.

REPORT OF CASES

During the past seven years this procedure has been performed on 40 patients at the Institute of Ophthalmology; of this number of operations it has been my privilege to perform or assist with 25—23 for exophthalmos and 2 for other reasons (Table 1).

Case 1.—A 3-year-old child came to the Vanderbilt Clinic in September, 1945, with exophthalmos of six months' duration. Examination with the child under ether anesthesia showed, in addition to the exophthalmos, 6 D. of right papilledema, corneal ulceration of the right eye, and

Table 1.—*Cases in Which Krönlein Operation Has Been Performed*

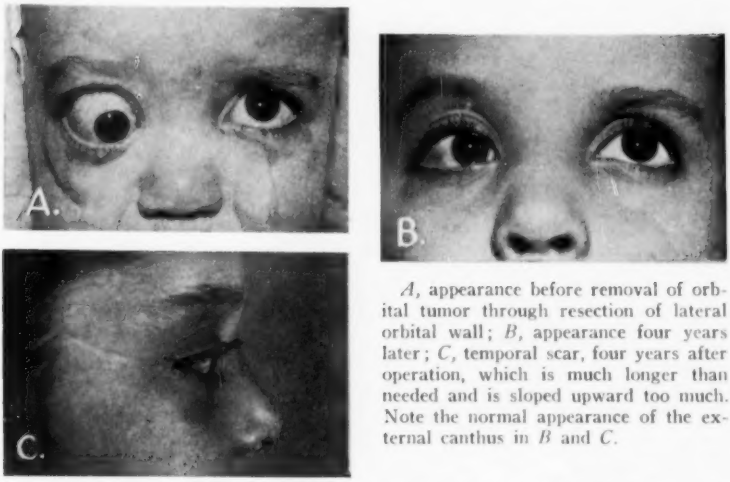
Condition Present	No. of Cases
Hemangioma (4 recurrent)	8
Tumor of optic nerve (3 gliomas, 1 meningioma)	4
Pseudotumor (granuloma)	3
Mixed tumor of lacrimal gland	2
Cysts (1 blood cyst, 1 lymph cyst)	2
Lymphosarcoma	1
Neurolemmoma (schwannoma)	1
Neurofibroma	1
Thyrotropic exophthalmos	1
Exposure of retrobulbar space (1 case for removal of a Cysticercus organism from eye and 1 case for ligation of the ophthalmic artery)	2
Total	25

optic atrophy of the left eye. An x-ray examination showed enlarged optic canals, the right being 8 by 8 mm. and the left 6 by 6.5 mm. An encephalogram was normal. A clinical diagnosis of glioma of the right optic nerve with probable involvement of the optic chiasm was made, but the neurosurgeon who examined the child declined to operate because of the possibility of destroying the sight of the left eye should a chiasmal extension be found and excised.

On Oct. 15, 1945, a large tumor of the optic nerve, measuring approximately 35 by 20 by 20 mm., was excised without difficulty, after resection of the lateral wall of the right orbit. The child made an uneventful recovery (Fig. 20). Four years after the operation an x-ray examination showed that the optic canals had decreased in size, the right then being 5 by 7 mm. and the left 4.7 by 7 mm. When last seen, five and one-half years after the operation, the child was living and well.

Case 2.—A 14-year-old boy came to the Vanderbilt Clinic in April, 1939, complaining of poor vision of the right eye of one year's duration. At that time the vision was 20/100 in the right eye and 20/20 in the left eye; the right eye was proptosed 3 mm., and the right optic nerve head showed primary atrophy. An x-ray examination demonstrated enlargement of the right optic canal, the right being 11 mm. and the left 5 mm. in diameter. A clinical diagnosis of glioma of the right optic nerve with intraorbital, and probably intracranial, involvement was made. A right frontal craniotomy revealed an intracranial tumor of the right optic nerve extending into the chiasm about 5 mm. Because the tumor involved the chiasm, a biopsy specimen only was taken. Biopsy confirmed the diagnosis of glioma of the optic nerve.

Ten years later the patient returned to the eye department of the Vanderbilt Clinic with 15 mm. of exophthalmos of the right eye (Fig. 21), no light perception in the right eye, 20/20



A, appearance before removal of orbital tumor through resection of lateral orbital wall; *B*, appearance four years later; *C*, temporal scar, four years after operation, which is much longer than needed and is sloped upward too much. Note the normal appearance of the external canthus in *B* and *C*.

Fig. 20.—Glioma of right optic nerve; right papilledema of 6 *D.*; left optic atrophy; enlargement of both optic canals (x-ray), and right exophthalmos, in child 3½ years old.

Fig. 21.—Glioma of right optic nerve, with 15 mm. of right exophthalmos, right optic atrophy, and no light perception in right eye.

A and *C*, appearance before removal of optic nerve tumor through a modified Krönlein operation; *B* and *D*, excellent cosmetic result three and a half years after operation. Note the short, inconspicuous scar and the normal appearance of the external canthus after operation.

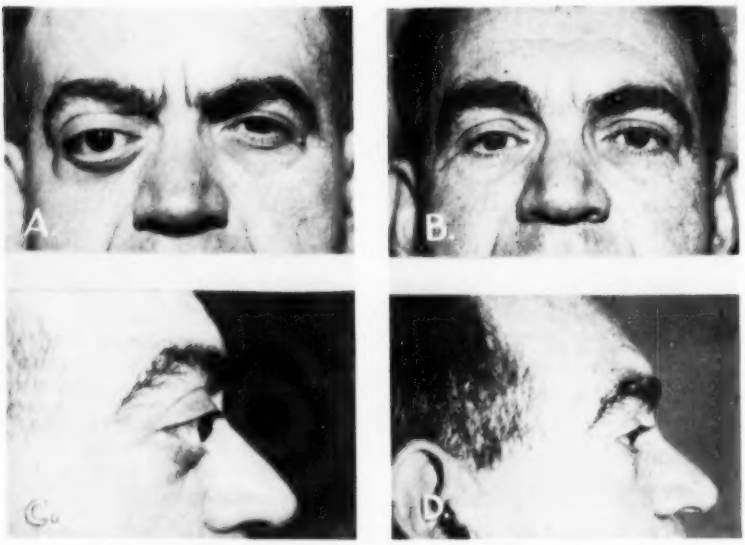
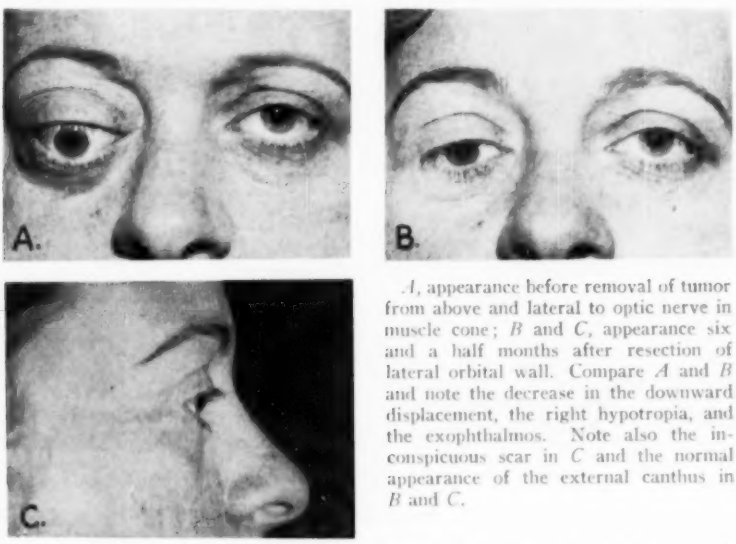


Fig. 22.—Hemangioma of the right orbit of 8 to 10 years' duration, producing 10 mm. of exophthalmos with downward displacement of the globe.

A and *C*, appearance before operation; *B* and *D*, appearance 21 months after removal of tumor from the muscle cone above optic nerve. Compare *A* and *B* and note that the right eye has assumed its normal position vertically; also compare *C* and *D* and note the marked reduction in the exophthalmos, the inconspicuous scar, and the normal contour of the external canthus.



A, appearance before removal of tumor from above and lateral to optic nerve in muscle cone; *B* and *C*, appearance six and a half months after resection of lateral orbital wall. Compare *A* and *B* and note the decrease in the downward displacement, the right hypotropia, and the exophthalmos. Note also the inconspicuous scar in *C* and the normal appearance of the external canthus in *B* and *C*.

Fig. 23.—Recurrent hemangioma of right orbit producing downward displacement of globe, marked right hypotropia, and 10 mm. of right exophthalmos.

vision in the left eye, and optic atrophy of the right eye. An x-ray examination showed that the right optic canal then measured 12 mm. in diameter, an increase of 1 mm. in 10 years. On June 22, 1949, a large glioma of the right optic nerve was removed by means of the technique described above. The histological diagnosis was astrocytoma of the optic nerve.

When the patient was last seen, three years after the orbitotomy, his cosmetic appearance was excellent (Fig. 21); vision in his left eye was 20/20, and his health was good.

CASE 3.—A 49-year-old man came to Dr. J. H. Dunnington in May, 1947, complaining of right proptosis of 8 to 10 years' duration. Examination showed 10 mm. of right exophthalmos (Fig. 22); vision, with glasses, of 20/40 in the right eye and 20/20 in the left eye, and horizontal retinal folds above the right optic disc. An x-ray examination showed increased soft-tissue density, slight enlargement of the right orbit, and evidence of increased intraorbital pressure. A clinical diagnosis of hemangioma was made and the retrobulbar space exposed by resection of the lateral wall of the right orbit. A large encapsulated tumor, measuring about 35 by 25 mm., was removed by finger dissection alone from above the optic nerve. The histological diagnosis was hemangioma.

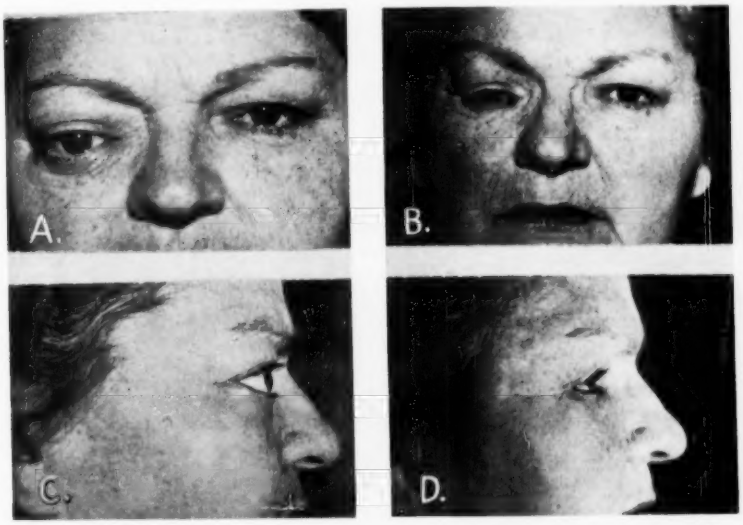


Fig. 24.—Recurrent hemangioma of right orbit, producing marked downward displacement, limitation of elevation, reduction of vision to 20/200, and right exophthalmos of 11 mm.

A and *C*, appearance before removal of the tumor from the muscle cone above the optic nerve; *B* and *D*, appearance four years later. Compare *A* and *B* and note that the right eye has returned to its normal position vertically; also compare *C* and *D* and note the marked decrease in the exophthalmos, the normal contour of the external canthus, and the short scar.

When the patient was last seen, three and a half years later, the exophthalmos (Fig. 22) and the retinal striations were gone; his extraocular movements were normal in all directions, and his vision in the right eye had improved to 20/20 with correction.

CASE 4.—A housewife, aged 49, saw Dr. J. H. Dunnington in November, 1949, because of right proptosis of three to four years' duration. Two years before, a large tumor (hemangioma) had been removed in three pieces through an external canthotomy, after which the exophthalmos was reduced for a time. Examination in 1949 showed 10 mm. of proptosis, downward displacement of the globe (Fig. 23), and marked weakness of elevation in the right eye. A clinical diagnosis of recurrent hemangioma was made.

On Nov. 23, 1949, a large tumor, measuring about 20 by 15 by 15 mm., was removed from above and lateral to the optic nerve within the muscle cone, after resection of the lateral orbital

A and *D*, appearance before resection of lateral orbital wall; *B* and *E*, appearance two weeks after removal of a long, firm mass from above and behind the globe outside the muscle cone; *C*, appearance six months after operation. Note that the marked edema of the lids and the temporal region two weeks after operation had completely disappeared six months later.

Fig. 25.—Mixed tumor of lacrimal gland producing 18 mm. of right exophthalmos and downward displacement of the globe.

wall. The anterior part of the tumor was bound down to the adjacent tissues—the result of the previous operation two years before. Histological diagnosis was hemangioendothelioma. When she was last seen, two and one-half years later (Fig. 23), the exophthalmos, the downward displacement of the globe, and the right hypotropia were much reduced.

CASE 5.—Mrs. L. S., aged 52, came to the Vanderbilt Clinic in September, 1948, because of poor vision and proptosis of the right eye. She stated that 15 years and, again, 2 years before, a tumor (hemangioma) had been removed from behind the right eye through the upper lid nasally.

Examination showed 10 mm. of exophthalmos and marked downward displacement of the right eye (Fig. 24). The vision was 20/200+1, in the right eye, and 20/30 in the left eye; the right disc showed 2 to 3 D. of papilledema, and a mass was palpable above the globe. An x-ray examination showed slight enlargement of the right orbit and increased soft-tissue density.

A clinical diagnosis of recurrent hemangioma was made, and on Sept. 29 the retrobulbar space was opened by means of resection of the lateral orbital wall. Palpation revealed a large irregular mass within the muscle cone above the optic nerve, extending from the apex of the orbit to the globe, with a finger-like projection extending forward between the globe and the nasal wall, the result of the previous operations. The tumor was removed by means of blunt and sharp dissection, during which the tumor collapsed, discharging bloody fluid. The histological diagnosis was hemangioma.

Four years later, the right exophthalmos and hypotropia were reduced (Fig. 24), vision was 20/70—1 in the right eye and 20/20+ in the left eye, and a moderate amount of right optic atrophy was present.

CASE 6.—A Negro, aged 68, saw Dr. Raymond Ingalls in December, 1949, because of right proptosis of four years' duration. His vision was 20/200 in the right eye and 20/50 in the left eye. A mass was palpable in the region of the right lacrimal gland, associated with 18 mm. of proptosis of the right eye and weakness of abduction and elevation in this eye. A biopsy specimen from the mass was diagnosed histologically as mixed tumor of the lacrimal gland.

Resection of the lateral orbital wall disclosed a long, firm tumor, extending from the region of the lacrimal gland to behind the globe. The mass was removed by blunt dissection, during which the capsule ruptured, discharging clumps of gray-colored, cheesy material.

Two weeks after operation considerable residual edema of the right lids and temple remained, but six months later this was completely gone (Fig. 25).

COMMENT

Complications During Operation.—1. Bleeding: Troublesome bleeding as a serious complication was conspicuous by its absence in each of these 25 cases, even though some of the vascular tumors ruptured during their removal. For example, in one patient with recurrent attacks of exophthalmos and ecchymosis, several cubic centimeters of dark blood was aspirated by needle puncture; therefore, a clinical diagnosis of orbital varix was made. But we hesitated to explore the orbit because of Benedict's || repeated warnings of the dire complications to be expected. However, when the patient suggested that the eye be enucleated for relief of pain, a lateral orbitotomy was done. This exposed a large dilated vein (diagnosed as cavernous hemangioma histologically) behind the globe. This was easily excised, with very little bleeding, by first ligating the feeder vessels. Therefore, lateral orbitotomy is a safe procedure for the removal of these vascular retrobulbar tumors.

In every case some sharp bleeding occurred after incising the skin and also after cutting the bone. The former was very easily controlled by hemostats; the latter usually stopped spontaneously, without the use of bone wax. In one case of aneurysm between the internal carotid artery and the cavernous sinus, an enlarged superior

|| References 9 to 13.

ophthalmic vein (the size of a lead pencil) was identified and retracted from the way and the ophthalmic and lacrimal arteries ligated, without mishap. Therefore, dangerous or uncontrolled bleeding does not seem to be a serious problem attending this procedure, probably because the excellent exposure achieved by this technique aids visual ligation of the vessels.

2. Injury to the Extraocular Muscles: In all these cases adequate exposure was usually achieved by retraction of the bone and the skin. When the tumor was not immediately visible, it was located by palpation and then visualized (even on the nasal side of the optic nerve) by retracting the lateral rectus muscle, the orbital fat, or the optic nerve.

If the tumor was encapsulated and not adherent to the adjacent structures, it was generally removed easily by blunt finger or scissors dissection. If, however, the tumor infiltrated the retrobulbar tissues or was adherent to the adjoining structures, its removal was more difficult. Under such conditions, damage to the extraocular muscles occurred during excision of the tumor in two cases and to the optic nerve and the extraocular muscles in one case. In each of these three cases the entire tumor was excised from the apex of the orbit with one snip of the scissors. In retrospect, it was felt that these complications could have been avoided had the cutting been done only under direct visualization, as advocated by Spaeth.[14]

3. Rupture of the Tumor: In six cases (two cysts, three hemangiomas, and one mixed tumor of the lacrimal gland) the tumor ruptured or partly collapsed during the operation. This made removal of the mass more difficult, but by application of small clamps to the sac of the tumor in a "hand-over-hand" manner the tumor was usually completely removed.

4. Failure to Find a Tumor: In one case of marked (10 mm.) unilateral proptosis of one year's duration with limitation of extraocular motility and diminishing vision, exploration of the orbit failed to reveal a tumor. In this case the extraocular muscles were enlarged, and a biopsy showed the histological picture of "thyrotropic exophthalmos."

Complications After Operation.—1. Vitreous Hemorrhage: This complication occurred in a 56-year-old man, presumably because of too much traction on the globe, in a case in which a large motor-driven circular bone saw was used to cut the bone. This complication did not occur with the Stryker bone saw, probably because less traction on the globe was necessary to gain adequate exposure.

2. Occlusion of the Central Retinal Artery: This complication occurred in a 39-year-old man with congenital syphilis and 13 mm. of exophthalmos. Operation disclosed an extensive retrobulbar hemangioma surrounding the lateral side of the optic nerve and extending from the apex of the orbit to the region of the lacrimal gland. It was thought that the occlusion in this case occurred because of the extensive manipulation necessary to remove the tumor.

3. Rounded Outer Canthus: In one case the external canthus was obtuse. This occurred because the upper and lower limbs of the external canthal ligament had not been properly anchored to the periosteum at the close of the operation.

4. Granulation Tissue at External Canthus: A small nodule of granulation tissue appeared at the external canthus after operation in one case. This was snipped off, leaving no deformity (Fig. 22).

5. Corneal Anesthesia with Neuroparalytic Keratitis: This complication occurred in one case in which the extraocular muscles were injured during removal of the tumor. Takats [15] found this complication in 6 of 55 Krönlein operations.

6. Temporary Weakness of Extraocular Muscles: In several cases ptosis with weakness of extraocular motility persisted for as long as six weeks. In other cases, in which this finding was present before operation, it persisted even though the exophthalmos was less. Takats [15] found permanent paralysis of the external rectus muscle in 2 of 55 operations, in some of which this muscle was severed to gain added exposure.

INDICATIONS FOR RESECTION OF THE LATERAL ORBITAL WALL

To list which of the 33 histological varieties of orbital tumors [11] are suitable for the Krönlein orbitotomy is impractical because the correct diagnosis is seldom made without first examining the tumor microscopically. Therefore, the decision to explore an orbit must be based almost entirely on the history and the clinical and laboratory findings.

This does not mean that one should not try to make a provisional histological diagnosis in every case before orbitotomy is done. As a matter of fact, Pfeiffer [16] has shown that a positive suggestive diagnosis of the histological nature of the tumor can be made in over 60% of the cases by the x-ray examination alone. When the x-ray report was combined with the history and the clinical findings, the correct histological diagnosis was made preoperatively in 64% of the cases reported here. Occasionally a general physical examination and certain other laboratory tests (basal metabolic rate determination, blood studies, etc.) may be a help in making the correct diagnosis. In other cases the histological diagnosis must be presumptive. This is especially true of primary malignant retrobulbar tumors.

In general, one should explore the retrobulbar space through a lateral orbitotomy under the following conditions:

1. When the vision of the exophthalmic eye is threatened by exposure keratitis or by damage to the optic nerve or retina.

2. When one has good reason to suspect a primary retrobulbar malignant tumor.

3. When the cosmetic appearance is distressing to the patient.

4. When added exposure of the retrobulbar space is necessary for the removal of foreign bodies, for ligation of vessels, or for removal of a Cysticercus cyst from the posterior pole of the eyeball.

5. When conservative treatment has failed. As pointed out by Foster,[17] one should not simply "iodize and temporize" or "irradiate and exenterate." To rely on the "sweet essence of time" while the exophthalmos progresses, until the cornea ulcerates or optic atrophy develops and the extraocular muscles become paralyzed, or life itself is lost, does not seem to be good medical practice. Therefore, the orbit should be explored before these complications develop.

Using the above criteria, a Krönlein orbitotomy was done on these 25 patients, for the following reasons: (1) for preservation of sight, 10 cases (7 cases of hemangiom, 3 cases of pseudotumor); for suspected malignant tumor, 8 cases (1 case of monocular exophthalmos associated with thyroid dysfunction, 2 cases of tumor of

the lacrimal gland, 2 orbital cysts, 1 lymphosarcoma, 1 neurolemmoma, 1 neurofibroma); for cosmetic reasons, 5 cases (1 hemangioma [Fig. 23], 4 tumors of the optic nerve [Figs. 21 and 22]), and for exposing the retrobulbar space, 2 cases (1 case of ligation of the ophthalmic and the lacrimal arteries in a patient with an internal carotid-cavernous sinus aneurysm, 1 case for removal of a Cysticerus cyst of the retina adjacent to the nerve head). In most of these cases there was more than one reason for doing the operation; for example, in 14 cases the exophthalmos was sufficiently great to justify the operation for cosmetic reasons.

As pointed out by Benedict¶ one should not explore the orbit from idle curiosity; the orbitotomy should afford ample working space, and the surgeon should be prepared to excise the whole tumor at one sitting. When the tumor is not easily extirpated and the possibility of a malignant growth cannot be ruled out, biopsy tissue for frozen section study may be taken, as recommended by Reese,# before proceeding with the complete removal of an infiltrative growth, for complete excision, accompanied, as it must be, by irreparable injury to the retrobulbar nerves, is not justified unless one is dealing with a malignant neoplasm.

CONTRAINDICATIONS TO RESECTION OF THE LATERAL ORBITAL WALL

It is difficult to make hard and fast rules as to when an orbit should not be explored because such rules, to be all-inclusive, would be extremely cumbersome to apply and would leave little opportunity for the exercise of sound surgical judgment. However, it would seem that when a positive clinical diagnosis can be made, a Krönlein orbitotomy is contraindicated under the following conditions: (1) when the tumor is anterior to the globe; (2) when the tumor extends into the retrobulbar space from adjacent structures (e. g., eyeball, pharynx, paranasal sinuses, or intracranial cavity); (3) when the tumor is metastatic (from the breast, stomach, prostate, bone or skin, etc.); (4) when a pseudotumor (granuloma) is present, except as a sight-saving measure; (5) when the exophthalmos is caused by certain systemic diseases, e. g., thyroid dysfunction, lymphomatous diseases (lymphosarcoma, lymphoma, Hodgkin's disease), Hand-Schüller-Christian disease, gumma, tuberculoma, Paget's disease, craniostenosis, hemophilia, or scurvy.

Occasionally one may be forced to remove a secondary tumor or a pseudotumor for the relief of pain, even though this does not change the ultimate prognosis.

When the tissues anterior to the globe are involved, the tumor should be excised by the anterior route; or when the retrobulbar space is invaded from adjacent tissues, the best approach to the tumor may be through the structures primarily involved. For example, if a mucocele or a malignant neoplasm in the paranasal sinuses invades the orbit, the otolaryngologist often is best qualified to excise the tumor; or if a meningioma, a fibroma, or an osteoma of the cranial cavity invades the orbit, the tumor should be removed by the neurosurgeon. The same may be said for some vascular tumors and some neurofibromas of the orbit which extended from the orbit to the cranial cavity. An exception may be gliomas of the optic nerve originating in the orbit and extending into the optic canal.

¶ References 9 through 13.

Reese, A. B.: Personal communication to the author.

KRÖNLEIN VS. TRANSCRANIAL APPROACH

Because the classic Krönlein operation tends to give inadequate exposure and because some retrobulbar tumors extend into the cranial cavity, certain authors * have advocated the transcranial approach for the removal of these tumors. For example, Dandy [18] contended that all orbital tumors should be extirpated transcranially, for the following reasons: 1. Forty-eight per cent of orbital tumors are meningiomas and 20% are cases of Schüller-Christian disease. 2. Intracranial tumors are also present in approximately 75 to 80% of orbital tumors. 3. "It is rarely possible before operation to be certain whether or not a tumor lies within the cranial cavity." 4. "Even for tumors confined to the orbit alone, this approach [the transcranial] has been found far superior to those hitherto used by ophthalmologists."

The combined experiences of several ophthalmologists with extensive experience with orbital tumors contradict Dandy's conclusions on all four counts. For example, his statement that 48% of orbital tumors are meningiomas is at variance with other reports on the incidence of orbital meningiomas as a cause of exophthalmos. Pfeiffer,[16] for instance, found only 13.3% of 105 orbital tumors to be meningiomas; Forrest,[27] 9.4% of 96 cases; Schreck,[28] 22% of 70 cases; Reese,[29] 7.9% of 251 cases; Drescher and Benedict,[30] 24.3% of 70 cases, and Offret,[31] 15.7% of 504 cases (Table 2).

Furthermore, in 20% of Dandy's cases the histological diagnosis was Schüller-Christian disease, despite the fact that none of these cases showed the triad of symptoms characteristic of this disease, namely, exophthalmos, defects of the membranous bones, and diabetes insipidus. In contrast to Dandy's 20%, Pfeiffer found 1.8%, Reese 0.4%, and Drescher and Benedict 1.4%, as the incidence of Schüller-Christian disease in exophthalmos. Thus, it is obvious that an outstanding neurosurgeon was mislead into believing that the incidence of orbital tumors referred to him was typical of the incidence of orbital tumors as seen by the ophthalmologist.

Dandy's statement that 75 to 80% of orbital tumors invade the cranial cavity also differs with the experience of other authors. For example, the operative findings in Pfeiffer's 105 orbital tumors showed that only 16% (17 tumors) invaded the cranial cavity. Likewise, in only 28.5% (10 cases) of Benedict and Love's 35 cases was there intracranial involvement.†

Thus, it would seem that Dandy's opinion, based as it was on a small, selected group of cases, does not justify the conclusion that 75 to 80% of orbital tumors invade the cranial cavity.

When an orbital tumor extends beyond the retrobulbar space, Pfeiffer [16] has shown that such extension without x-ray evidence is rare. Benedict and Love [10] stated that the x-ray examination was positive for extraorbital extension in all such

---

* References 6, 7, 9, 10, and 18 through 26. Woods, A. C., in discussion on Dandy [6] and in introduction of Dandy.[18]

† Pfeiffer's 17 tumors that invaded the cranial cavity comprised 2 of 14 meningiomas, 6 of 7 neurofibromas, 7 of 7 gliomas of the optic nerve, and 2 of 2 cases of Schüller-Christian disease. Benedict and Love's 10 intracranial tumors consisted of 4 of 10 meningiomas, 3 of 5 gliomas of the optic nerve (2 of which were not excised, for "then all sight would have been lost"), 1 of 3 epidermoids, 1 granuloma, and 1 of 2 neurofibromas).

TABLE 2.—*Incidence of Orbital Tumors as a Cause of Exophthalmos as Reported by Several Authors**

Type of Tumor	Pfeiffer [10]		Forrest [27]		Schreck [28]		Reese [29]		Drescher and Benedict [30]		Offret [31]		Dandy [18]	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Mucocele	18	17.14	0	0	0	0	0	0	0	0	0	0	0	0
Pseudotumor (granuloma)	16	15.23	0	0	12	17	34	13.5	0	0	0	0	1	4
Meningioma	14	13.3	9	9.4	15	22	20	7.96	17	24.28	76	15.07	12	48
Hemangioma (assorted)	12	11.42	12	12.5	12	17	50	19.9	17	24.28	93	18.45	0	0
Dermoid, oil and blood cysts	8	7.61	1	1.04	6	9	36	14.3	3	4.28	55	10.9	0	0
Assorted sarcomas	4	3.8	22	22.9	9	13	12	4.78	7	10	64	12.7	2	8
Neurofibroma, neuroma, etc.	9	8.57	10	10.4	1	1.4	12	4.78	1	1.4	47	9.32	0	0
Tumors of optic nerve	7	6.66	5	5.2	5	7	16	6.37	6	8.57	24	4.76	0	0
Mixed tumors of lacrimal gland	5	4.76	12	12.5	0	0	14	5.57	4	5.71	17	3.37	0	0
Lymphangioma	0	0	0	0	0	0	5	1.99	0	0	0	0	0	0
Myeloblastoma or myeloma	1	0.95	0	0	0	0	4	1.59	0	0	0	0	0	0
Hematoma (subdural or orbital)	1	0.95	0	0	0	0	3	1.19	0	0	0	0	0	0
Carcinoma	0	0	0	0	7	10	1	0.4	6	8.57	0	0	1	4
Osteoma	3	2.85	5	5.2	1	1.4	0	0	4	5.71	0	0	2	8
Lymphomatous tumors	2	1.8	12	12.5	0	0	36	14.3	4	5.71	103	20.27	0	0
Hand-Schüller-Christian disease	2	1.8	0	0	0	0	1	0.4	1	1.4	0	0	5	20
Lipoma	0	0	2	2.08	0	0	1	0.4	0	0	25	4.96	0	0
Fibrolipoma	0	0	2	2.08	0	0	0	0	0	0	0	0	0	0
Fibroma	0	0	2	2.08	0	0	1	0.4	0	0	0	0	1	4
Chondroma	0	0	1	1.04	0	0	0	0	0	0	0	0	0	0
Rhabdomyoma	0	0	1	1.04	0	0	0	0	0	0	0	0	0	0
Dermolipoma	0	0	0	0	0	0	1	0.4	0	0	0	0	0	0
Giant cell tumor of tendon sheath	0	0	0	0	0	0	1	0.4	0	0	0	0	0	0
Mixed neurogenic tumor	0	0	0	0	0	0	1	0.4	0	0	0	0	0	0
Medulloblastoma	0	0	0	0	0	0	1	0.4	0	0	0	0	0	0
Osteopathic fibrosis	0	0	0	0	1	14	0	0	0	0	0	0	0	0
Gumma	2	1.8	0	0	0	0	0	0	0	0	0	0	0	0
Teratoma	1	0.95	0	0	1	14	0	0	0	0	0	0	0	0
Adamantinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chondromyxoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fat necrosis	0	0	0	0	0	0	1	0.4	0	0	0	0	0	0
Osteomatous cyst	0	0	0	0	0	0	0	0	0	0	0	0	1	4
	105		86		70		251		70		504		25	

* Ninety-five of Pfeiffer's [10] 200 cases of exophthalmos have been eliminated from this Table, mostly because the lesion causing the exophthalmos was not tumorous; that is, there were 14 cases of craniostenosis, 12 cases of exophthalmos associated with thyroid dysfunction, 9 cases of oculomotor paralysis, 2 cases of secondary orbital involvement from the choroid, 7 cases of deformity of the orbits, 6 cases of arteriovenous aneurysm between the internal carotid artery and the cavernous sinus, 4 cases of malignant growth from the paranasal sinuses, 4 cases of saccular aneurysm of the internal carotid artery, 4 cases of abscess of the orbit, 3 cases of Paget's disease, 2 cases of basal-cell epithelioma, 3 cases of congenital coloboma cyst of the eyeball or retinocele, 2 cases of myopia, 1 case of trichinosis, 1 case of osteitis fibrosa cystica, 1 case of iodized oil (Lipiodol) in the orbit, and 20 cases in which operation was refused.

Also, 88 of Forrest's [27] 184 cases of primary tumors of the orbit were eliminated because of the absence of exophthalmos: 17 cases of lipoma, 12 cases of hemangioma, 1 case of angiosarcoma, 13 cases of tumors of the hematopoietic system, 13 cases of mixed tumors of the lacrimal gland, 7 cases of neurofibroma, 8 cases of meningioma, 16 cases of dermoid, and 1 case of teratoma.

Schreck's [28] 70 cases of primary tumors of the orbit, in which the diagnosis was confirmed by operation or by histological study, are included in this tabulation.

In only 70 of Drescher and Benedict's [30] 177 cases of exophthalmos are the tumors considered primary in the orbit. This includes six cases of metastatic orbital tumors because these lesions act as primary tumors and because the diagnosis usually is not made until after the tumor has been studied histologically.

Offret's [31] figures include those of Schreck,[28] Dandy,[18] Reese,[4] and Forrest [27] and seven other reports, including his own, so that his tabulation doubtless includes some cases without exophthalmos.

cases, except in two cases of meningioma without exophthalmos and one case of astrocytoma of the optic nerve. Thus, the x-ray failed to show an extraorbital extension in only one of their 33 cases of exophthalmos.‡

Therefore, it must be comparatively rare to have an intracranial extension of an orbital tumor which does not give some suggestion of such extension by careful preoperative x-ray and clinical studies.

Dandy's hope of completely excising these tumors by the transcranial approach had apparently not been fully realized, because he considered only 3 of his 25 tumors to be benign or to have been completely removed. In one (Case 15) deroofing the orbit failed to expose the tumor. Here the exophthalmos continued to increase postoperatively.§

In six of his cases, in which the tumor was confined to the orbit, it is doubtful whether the final result achieved by deroofing the orbit was better than it would have been had resection of the lateral orbital wall been done. For example, a tumor "the size of a pea" in front of the optic canal (Case 1) could have been as easily removed by the modified Krönlein approach. Also, a bony cyst of the floor and nasal wall, the removal of which exposed the patient to intracranial infection and required two craniotomies (Case 4), could have been removed more easily and safely by the lateral approach. The same may be said for a round-cell sarcoma lying lateral to the optic nerve (Case 6) and for a granulomatous tumor (diagnosed as Schüller-Christian disease, Case 10) lying under the optic nerve. A carcinoma of the apex of the orbit (Case 24), with clinical evidence of intracranial extension—deafness, complete anosmia, blindness, ptosis, limited extraocular motility—which was found at operation to be confined to the orbit, and another tumor (diagnosed as pseudotumor at one institution and as Schüller-Christian disease at another), which infiltrated the tissues above the cone of muscles so extensively that its complete removal was impossible, would doubtless have been difficult to remove by any method without causing irreparable damage to the retrobulbar tissues. Thus, a critical analysis of Dandy's results casts considerable doubt on whether the transcranial approach is far superior to the approach hitherto used by ophthalmologists for the removal of tumors confined to the orbit alone.

Dandy implies that because gliomas of the optic nerve tend to invade the cranial cavity, these tumors should always be excised intracranially. However, his results would tend to prove just the opposite, because in two of his four cases in which an attempt was made to remove only a part of the intracranial extension of the tumor both patients died within 15 days. Had the orbital part of these tumors only been removed through an orbital approach, these two patients might still be alive. For example, Hudson [34] reported, in his classic review of 1912, five cases of glioma of the optic nerve in which no recurrence of the tumor had occurred after 15 to 24 years, even though incompletely removed. He concluded that the intracranial exten-

‡ In the two cases of meningioma the Krönlein operation was definitely contraindicated in the absence of exophthalmos; in the case of the astrocytoma with orbital and intracranial involvement and with a normal optic canal (a rare finding) two tumors were probably present—one in the orbit and one in the cranial cavity—a not unusual occurrence according to Davis.[8] Here a Krönlein operation would have been less hazardous than the transcranial approach, which of itself carries a mortality of 4.1% in good hands, according to Dandy.[18]

§ Reese [29] knows of two other cases in which a transcranial approach failed to locate an orbital tumor. Drell [32] and Stallard [33] each reported a similar case.

sion of the tumor either became stationary or is so slowly progressive that the patient generally succumbs to some commoner ailment. Knapp [35] was of a similar mind. In 1941 || he reported three cases of glioma of the optic nerve in which only the orbital part of the tumor was removed, with preservation of the globe, through a Krönlein operation. All the patients were alive and well with good vision in the opposite eye 15 to 18 years later, even though the optic canals were found to be enlarged on x-ray examination at the time of operation. Davis [3] reported a similar case, in which the patient was alive eight years after exenteration of the orbit. Furthermore, our three patients with glioma of the optic nerve were alive and well with good vision in the opposite eye when last seen five and a half, four, and three and a half years after operation. In two of the cases postoperative x-ray pictures showed that the enlarged optic canals had decreased in diameter. This observation, plus the absence of symptoms of intracranial tumor, would tend to indicate that the growth of these tumors had been discouraged. In this connection, Verhoeff [36] stated that there is no evidence to indicate that these tumors ever recur, even after their incomplete removal. Commenting on the poor results obtained by the intracranial approach, Bailey ¶ said: "No one who knows how little can be accomplished by the intracranial route could be enthusiastic about the transfrontal route." Martin and Cushing,[37] after unhappy experiences with removal of optic nerve and chiasmal gliomas, concluded that Dandy was "overenthusiastic" with regard to the operability of these gliomatous tumors.

Therefore, there is little in Dandy's book to substantiate his claim that all orbital tumors should be removed by the transcranial approach. There is much indirect evidence, however, to indicate that orbital tumors which are confined to the orbit should be removed through an orbital approach. On the other hand, he has shown conclusively that certain tumors which invade the cranial and the orbital cavities can be removed by craniotomy. However, one should be ever mindful of Naffziger's [7] admonition, "Orbital decompression, although carrying little risk, is a procedure of such magnitude that it must be reserved for cases of considerable gravity."

SUMMARY AND CONCLUSIONS

1. The anatomy of the lateral orbital wall is ideally suited for orbitotomy, because (*a*) it is the most accessible and the easiest to resect of the four orbital walls, (*b*) resection of 1 sq. in. (6.5 sq. cm.) of this wall gives greater exposure of the retrobulbar space than a similar amount of resection of any of the other walls can give, and (*c*) no important periorbital structures are endangered by the operation.

2. The operation sponsored here has the following advantages over the classic Krönlein operation: (*a*) The initial incision is shorter and more direct; (*b*) the tedious task of reflecting the periosteum is rendered unnecessary; (*c*) the Stryker oscillating saw makes the procedure easier, quicker, and safer; (*d*) a less conspicuous and shorter scar results, and (*e*) no permanent damage to the nerve supply of the orbicularis muscle occurs.

3. Complications can be reduced to a minimum by (*a*) eliminating excessive traction on the globe and unnecessary manipulation of the retrobulbar tissues, (*b*)

|| Knapp, A., in discussion on Dandy.[6]

¶ Bailey, P., in discussion on Davis.[3]

extirpating the tumor only by blunt dissection whenever possible, (*c*) using sharp dissection only under direct visualization, and (*d*) using reasonable care in closing the wound.

4. The operation is indicated (*a*) when the vision of an exophthalmic eye is threatened, (*b*) when a primary retrobulbar malignant neoplasm is suspected, (*c*) when the cosmetic appearance is distressing to the patient, (*d*) when conservative treatment has failed, and (*e*) when added working space is needed for the removal of a Cysticercus cyst from the posterior pole of the globe or for ligation of vessels in the retrobulbar space.

5. The operation is contraindicated (*a*) when an orbital tumor is anterior to the globe, (*b*) when the retrobulbar space is invaded from adjacent structures, (*c*) when the tumor is metastatic, (*d*) when a pseudotumor (granuloma) is present, and (*e*) when the exophthalmos is caused by certain systemic diseases.

6. The transcranial approach should not be used for the removal of all orbital tumors because (*a*) less than 30% of these tumors invade the cranial cavity, (*b*) the orbital tumor is not always found by this approach, (*c*) the risk of infection from the ethmoid cells endangers the life of the patient unnecessarily, (*d*) the mortality rate of the operation, even in good hands, is 4.1%, and (*e*) "the procedure is of such magnitude that it must be reserved for cases of considerable gravity" (Naffziger [7]).

7. Gliomas of the optic nerve, even with intracranial extension, should be excised by the lateral rather than by the intracranial approach, because (1) even though not completely removed, they do not recur, and (2) intracranial extirpation endangers the sight of the other eye and the patient's life, especially if the chiasm is involved, because the hypothalmos does not tolerate trauma well.

8. Certain other tumors, with intracranial involvement, such as meningiomas, neurofibromas, endotheliomas, sarcomas, osteomas, fibromas, and vascular tumors, the intracranial extension of which can generally be ascertained by complete ophthalmological, neurological, and roentgenological studies, should be removed by the joint efforts of the ophthalmic and the neurological surgeon.

The attending staff of the Institute of Ophthalmology, Presbyterian Hospital, permitted the publication of the case reports, and the art and photography departments cooperated in the study.

REFERENCES

1. Krönlein: Zur Pathologie und Behandlung der Dermoidcysten der Orbita, Beitr. klin. Chir. **4**:149, 1888.

2. Benedict, W. L.: Removal of Orbital Tumors, Surg., Gynec. & Obst. **58**:383-389, 1934.

3. Davis, F. A.: Primary Tumors of Optic Nerve, Arch. Ophth. **23**:735-821; 957-1018, 1940.

4. Reese, A. B.: Orbital Tumors and Their Surgical Treatment, Am. J. Ophth. **24**:386-394; 497-502, 1941.

5. Knapp, H.: A Case of Carcinoma of the Outer Sheath of the Optic Nerve Removed with Preservation of the Eyeball, Arch. Ophth. **4**:323-354, 1874.

6. Dandy, W. E.: Results Following Transcranial Operative Attack on Orbital Tumors, Arch. Ophth. **25**:191-216, 1941.

7. Naffziger, H.: Exophthalmos and Its Surgical Treatment, Am. J. Ophth. **32**:857-858, 1949.

8. Swift, G. W.: Malignant Ophthalmos and Operative Approach, West. J. Surg. **43**:119-126, 1935.

9. Adson, A. W., and Benedict, W. L.: Hemangioendothelioma of the Orbit: Removal Through Transcranial Approach, Arch. Ophth. **12**:484-492, 1934.

10. Benedict, W. L., and Love, J. G.: Transcranial Removal of Intraorbital Tumors, J. A. M. A. **129**:777-784, 1945.

11. Benedict, W. L.: Surgical Treatment of Tumors and Cysts of the Orbit, Am. J. Ophth. **32**:763-773, 1949.

12. Benedict, W. L.: Diseases of the Orbit, Am. J. Ophth. **33**:1-10, 1950.

13. Benedict, W. L.: Diagnosis of Orbital Tumors, J. A. M. A. **126**:880-884, 1944.

14. Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, Ed. 4, Philadelphia, Lea & Febiger, 1948.

15. Takats, G.: Surgery of the Orbit, Arch. Ophth. **8**:259-268, 1932.

16. Pfeiffer, R. L.: Roentgenography of Exophthalmos with Notes on the Roentgen Ray in Ophthalmology, Am. J. Ophth. **26**:724-740; 816-833; 928-942, 1943.

17. Foster, J.: The Surgery of Orbital Tumors, XVI Conc. Ophth., London **2**:1246, 1950.

18. Dandy, W. E.: Orbital Tumors: Results Following the Transcranial Operative Attack, New York, Oskar Piest, 1941.

19. Craig, W., and Gogela, L. J.: Intraorbital Meningiomas: Clinicopathologic Study, Am. J. Ophth. **32**:1663-1668, 1949.

20. Löhlein, W., and Tönnis, W.: The Surgical Treatment of New Growths Beyond the Optic Foramen, von Graefes Arch. Ophth. **149**:318-354, 1949.

21. Fralick, F. B.: The Orbit: Review of Literature, 1950, Arch. Ophth. **44**:437-453, 1950.

22. Buffat, J. D.: Neurosurgical Treatment of Tumors of Optic Nerve, Rev. méd. Suisse rom. **69**:511-522, 1949.

23. Standal, B.: Neurinoma of the Orbit, Acta ophth. **28**:49-70, 1950.

24. Heimburger, R. F.; Oberhill, H. R.; McGarry, H. I., and Bucy, P. C.: Intraorbital Aneurysm, Arch. Ophth. **42**:1-13, 1949.

25. Jackson, Harvey: Orbital Tumors, Brit. J. Ophth. **28**:472-476, 1944.

26. Jackson, Harvey: Orbital Tumors, Proc. Roy. Soc. Med. **38**:587-593, 1945.

27. Forrest, A. W.: Intraorbital Tumors, Arch. Ophth. **41**:198-232, 1949.

28. Schreck, E.: Zur Klinik und pathologischen Anatomie der Orbitaltumoren, Klin. Monatsbl. Augenh. **103**:1-44, 1939.

29. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951.

30. Drescher, E. P., and Benedict, W. L.: Asymmetric Exophthalmos, Arch. Ophth. **44**:109-128, 1950.

31. Offret, Guy: Les tumeurs primitives de l'orbite, Paris, Masson & Cie, 1951.

32. Drell, M.: Orbital Neoplasm, Am. J. Ophth. **27**:543, 1944.

33. Stallard, H. B.: A Plea for Lateral Orbitotomy (Krönlein Operation), Brit. M. J. **1**:408-409, 1947.

34. Hudson, A. C.: Primary Tumors of Optic Nerve, Roy. Lond. Ophth. Hosp. Rep. **18**:317, 1910-1912.

35. Knapp, A.: On the Intracranial Extension of Optic Nerve Tumors, Contributions of Ophthalmic Science, Menasha, Wis., George Banta Publishing Company, 1926.

36. Verhoeff, F. H.: Primary Intraneural Tumors of the Optic Nerve, Arch. Ophth. **51**:239, 1922.

37. Martin, P., and Cushing, H.: Primary Tumors of the Chiasm and Optic Nerve in Their Intracranial Portion, Arch. Ophth. **52**:209, 1923.

38. Wiener, M., and Scheie, H. G.: Surgery of the Eye, New York, Grune & Stratton, Inc., 1952.

USE OF RADIOACTIVE PHOSPHORUS IN DETECTION OF INTRAOCULAR NEOPLASMS

I. J. EISENBERG, M.D.

I. H. LEOPOLD, M.D.

AND

D. SKLAROFF, M.D.

PHILADELPHIA

IN THE past few years attempts have been made to detect intracranial neoplasms with radioactive isotopes.* One of these was diiodofluorescein.[2] This isotope has been shown to be of value in the detection of brain tumors. Since the retina and associated structures are closely allied to the brain, the possibility of detecting intraocular neoplasms by this technique was investigated.

The initial results obtained in the first three patients were unsatisfactory. It was felt that diiodofluorescein failed because it emitted gamma rays. Such rays mask detection of any concentration in a tumor of the eye, for the following reasons:

1. The volume of an intraocular neoplasm rarely occupies more than one-fourth of the globe.

2. Diiodofluorescein is taken up by normal tissue, as well as by pathologic tissue.

3. Gamma rays have marked penetrating power in tissue.

It appeared that a substance emitting pure beta rays would be preferable, as these rays are absorbed by a few millimeters of tissue and therefore might eliminate the masking effect by normal cells (Fig. 1).

This "ideal" isotope should have the following characteristics:

1. The safety factor to the patient should be large.

2. Tumor cells must absorb a measurably greater amount than is taken up by normal cells.

3. The half-life must be long enough to make transportation and handling practical, but not so long as to become dangerous either to patients or in disposal.

4. The disintegration rays should be neither too powerful nor too weak.

Radioactive phosphorus, commonly known as P^{32}, approached the ideal isotope, for the following reasons:

1. The safety factor is adequate, for the amount necessary to detect an intraocular lesion is 0.5 mc., or approximately 300 mrem (milliroentgen equivalents),

This research was performed under Atomic Energy Commission Authority 17818.

From the Department of Research, Wills Eye Hospital, and Albert Einstein Medical Center (Northern Division).

Read before the Section on Ophthalmology at the 102nd Annual Meeting of the American Medical Association, New York, June 2, 1953.

* References 1 and 2.

which is the amount of total body radiation permissible per week.[7] A review of the literature for the last 15 years failed to reveal a report of any ocular complications from the use of radioactive phosphorus in greater concentrations than we were contemplating.

2. There is a detectable difference between the concentration of P^{32} in normal tissue and that in neoplastic tissue.

In 1940, Marshak [3] reported that the uptake of phosphorus by cells is due not to simple diffusion but to actual chemical metabolism. He also showed that the greater the metabolic activity, the greater the phosphorus concentration, and that this concentration does not depend on the histology of the cells. Kenny and co-workers,[4] in 1941, reported that tumor cells in osteogenic sarcoma showed as much as 12 times the concentration of P^{32} as normal cells.

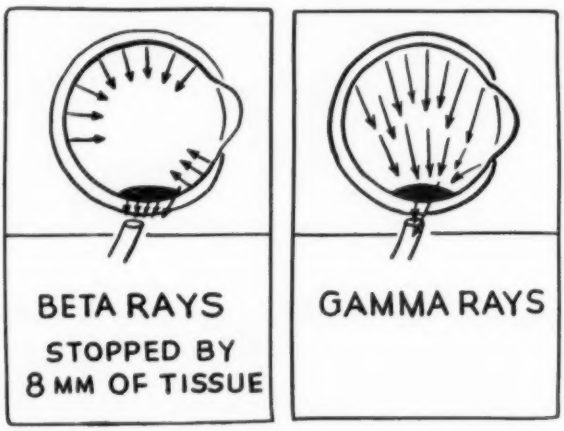


Fig. 1.—Schematic illustration of the masking effect of gamma rays.

Marinelli,[5] in 1942, showed that melanoma of the skin gave over seven times the concentration demonstrable in normal skin.

Low-Beer and co-workers,[6] in 1946, reported that the concentration of P^{32} at any given time depends upon the cellular activity of the tissues involved. Thus, malignant cells showed a greater concentration than normal cells. In this paper he also reported a positive concentration of P^{32} in breast carcinoma.

In 1950 Silverstone and colleagues reported on the successful use of P^{32} in 33 cases of brain tumor (after the skull was opened).

The third characteristic of the ideal ocular radioisotope is satisfied by the half-life of P^{32}. This is 14 days, which makes for ease in handling and disposal.

The disintegration rays have an energy which permits maximal penetration of approximately 8 mm. of tissue, thereby helping to eliminate the masking effect of the radiation emitted by normal cells.

After the use of P^{32} had been decided on, the next problem was to get a detector, or Geiger counter, small enough and yet sensitive enough to pick up the

differences in concentration. This was accomplished successfully by Thomas and co-workers,[8] as reported in 1952. They described the use of a small Geiger counter for the detection of intraocular tumors.

Using P^{32}, we sought in this investigation to answer the following problems:

1. What variations in concentration are found in the normal eye?

2. What should be considered a positive concentration as compared with the normal eye?

3. What effect would intraocular lesions other than neoplasms have on the concentration of P^{32}?

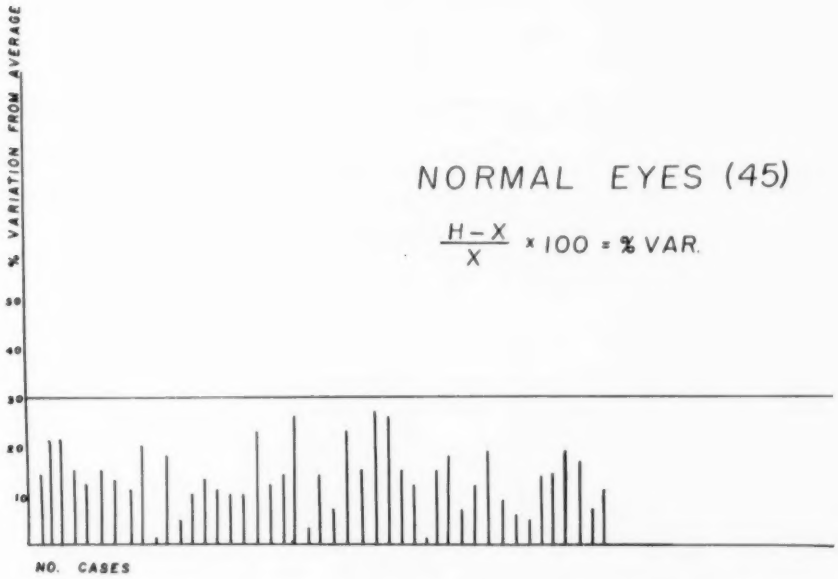


Fig. 2.—Forty-five normal eyes, all showing a variation of under 30% from the average of the normal eye. *H* represents the highest count per minute in the normal eye; *X* represents the arithmetic mean of the normal eye.

The technique was as follows:

1. A dose of 500 mc. of radioactive phosphorus was injected intravenously.

2. After an interval of 60 minutes a count was taken over the skin of the lobe of an ear and was recorded as the number of discharges per minute. (This figure is used only as a background.)

3. The eye was mapped out in four quadrants and each quadrant numbered in clockwise direction. A count for one minute was taken over each quadrant of the normal eye, the counter having been placed near the limbus.

4. With an ophthalmoscope, the intraocular lesion was visualized, and if possible an attempt was made to place the counter directly over the lesion. Several counts were taken over this locality, and an average count per minute was determined.

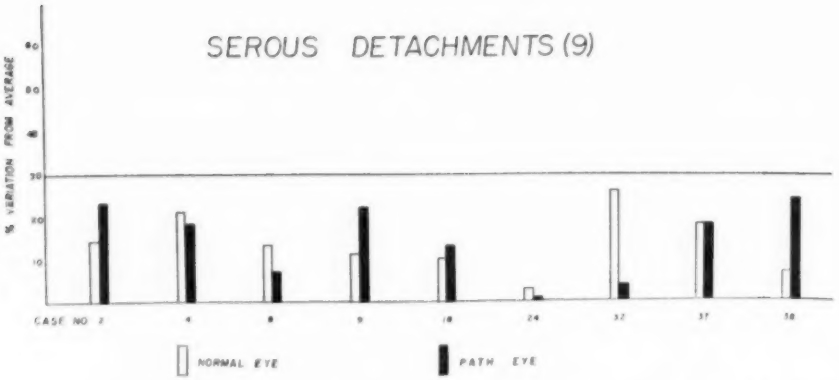


Fig. 3.—Nine cases of serous detachments of the retina showing a variation of under 30% from the average of the normal eye.

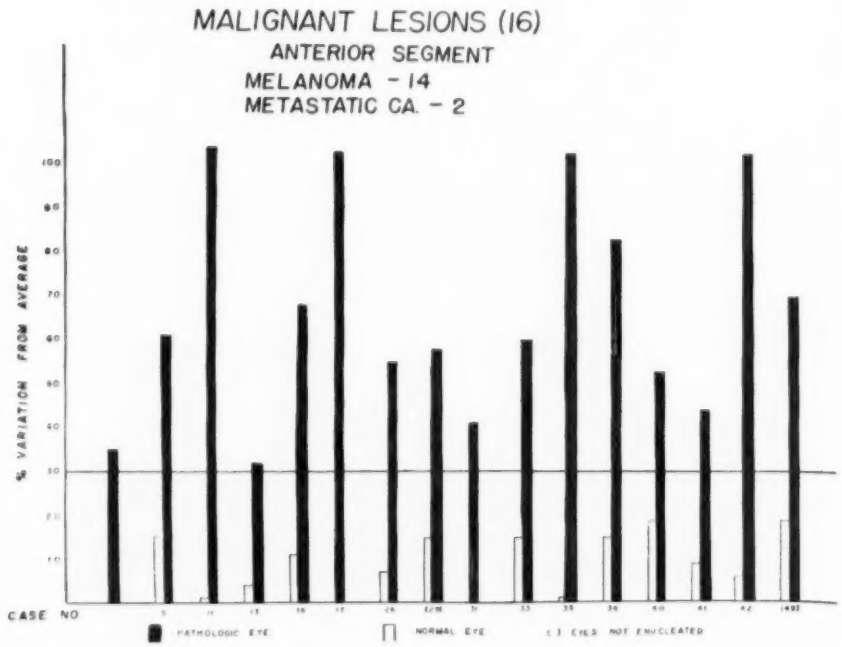


Fig. 4.—Sixteen malignant lesions, 14 of which were confirmed by histopathologic section, in the anterior segment of the globe, showing a variation in concentration of over 30%.

Case 1: A one-eyed patient with a melanoma of the iris and ciliary body. The uninvolved portion of the globe therefore was used as a control.

Case 17: A bilateral metastatic carcinoma from the breast. Therefore no normal eye was present to use as a comparison. In this case the concentration in the lobe of the ear was taken as a tentative normal value.

Counts were made and recorded as the number of ionizing discharges detected per minute. The percent variation of the highest reading in the normal eye from the average for the normal eye was determined by the following formula:

$$\frac{Hn - X}{X} \times 100 = \% \text{ variation} \quad (1)$$

where Hn is the highest reading in the normal eye and X, the arithmetic mean for the normal eye.

The percent variation of the highest reading in the pathologic eye from the average in the normal eye was also determined by the following formula:

$$\frac{Hp - X}{X} \times 100 = \% \text{ variation} \quad (2)$$

where Hp is the highest reading in the pathologic eye.

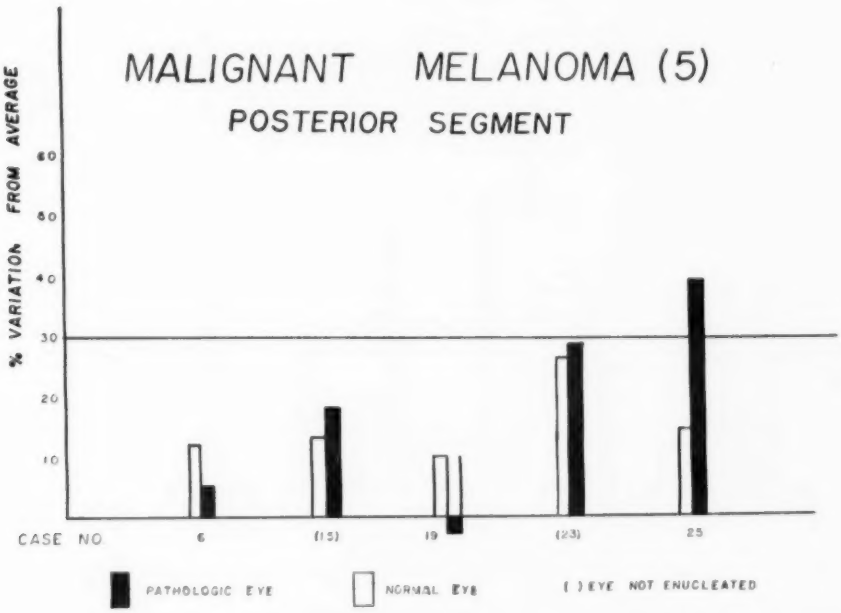


Fig. 5.—Five cases of malignant melanomas in the posterior segment of the globe.

Case 6: Histopathologic diagnosis of amelanotic melanoma with a history of being under observation for at least five years without signs of growth.

Case 15: Division of clinical opinion as to whether or not the lesion is malignant. To date eye has not been enucleated.

Case 23: Eye not enucleated to date. Clinical diagnosis is melanoma of the disc.

Case 25: Malignant melanoma of the macula.

Using the above data (Fig. 2), it was found that in 49 normal eyes the variation from the average was less than 30%. Therefore, it was assumed that if the variation was 30% or more it would be considered a positive concentration.

In this manner nine cases with a clinical diagnosis of serous retinal detachments were studied. None showed a variation of 30% or more (Fig. 3).

In 14 cases of malignant melanoma (Fig. 4), when the tumor was accessible to the counter (at or anterior to the equator of the globe as shown by enucleation), all showed a concentration at least 30% greater than the average normal.

Two cases of metastatic carcinoma (Fig. 4) also showed a positive concentration of P^{32}.

Of five cases of solid detachment (Fig. 5) posterior to the equator, one showed a concentration greater than 30%, one a concentration of 29%, and three a concentration less than 25%.

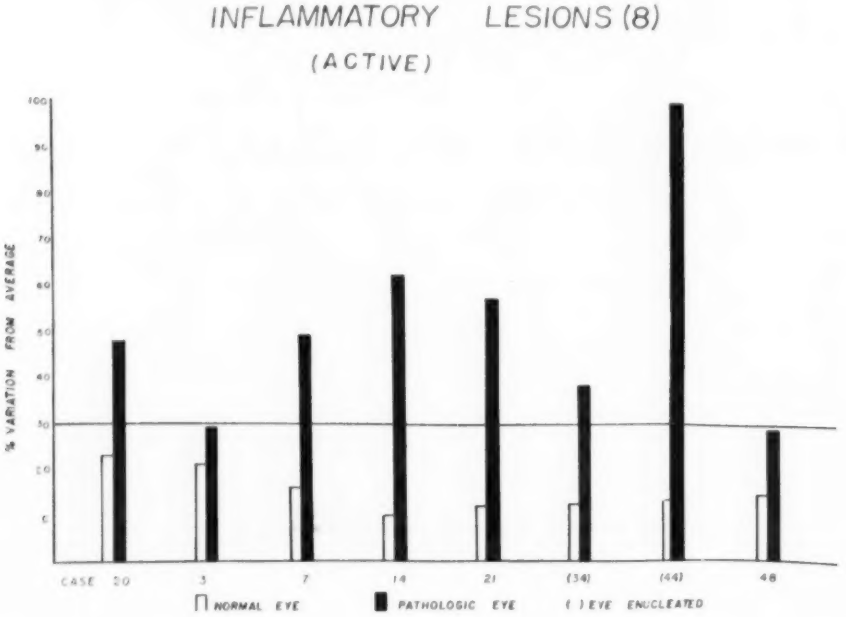


Fig. 6.—Eight cases of active inflammatory lesions in the anterior or posterior segment of the globe.

Case 34: Enucleation of the eye because no light perception was present and there was some suspicion of a neoplasm. Gross section revealed that most of the vitreous was replaced by what appeared to be inflammatory tissue (histopathologic diagnosis not yet available).

Case 44: Eye enucleated because it was blind and painful following recent trauma. Gross section revealed a large vitreous hemorrhage with inflammatory tissue (histopathologic diagnosis not yet available).

The eye showing a concentration of over 30% (Case 25) was proved to have a malignant melanoma of the macula.

The eye showing a concentration of 29% (Case 23) is considered to have a malignant melanoma near the disc. To date the eye has not been enucleated.

One of the negative results are obtained in an eye (Case 6 of this series) with a history of a tumor mass which had not grown for the five years that it had been under observation. Histologic study revealed it to be an amelanotic melanoma.

Another negative result occurred in Case 15, in which opinion is still divided as to whether or not the tumor is a malignant melanoma. This eye has not been enucleated.

Eight eyes with active anterior or posterior uveitis were tested. Six showed a concentration of over 30% and two a concentration of under 30% (Fig. 6).

In three cases of malignant melanoma of the iris or ciliary body the P^{32} uptake was more than 30%.

Of three cases of clinically benign tumors (nevus of the iris and melanoma [benign] of the anterior choroid), none showed a variation over 30%.

In five cases of hemorrhage into the vitreous or choroid not due to or associated with inflammation or neoplasm as far as we could clinically ascertain, the results were all under 30%.

In one case of phthisis bulbi the uptake was more than 30%.

The data of all tested eyes have been summarized in Table 1 and Table 2.

TABLE 1.—*Analysis of Reading on Forty-Nine Cases (P^{32} Concentration)*

	Total	Positive	Negative	Eyes Enucleated
Total cases of melanoma (malignant)	19	15	4	16
Anterior segment				
Choroid	11	11	0	10
Iris and ciliary body	3	3	0	3
Posterior segment				
Choroid	4	1	3	3
Disc	1	0	1	0
Total cases of melanoma (benign)	3	0	3	0
Iris	2	0	2	0
Choroid	1	0	1	0
Metastatic carcinoma	2	2	0	1
Uveitis (active)	8	6	2	2
Serous detachment	9	0	9	0
Choroidal hemorrhage or hemorrhage in vitreous	5	0	5	0
Staphyloma of globe	1	0	1	1
Phthisis bulbi	1	1	0	1
Absolute glaucoma	1	0	1	0

COMMENT

This study revealed several points of interest.

It was noticed that while a count was being taken in the quadrants of the normal eye, an abnormally high count would occasionally be recorded. But if the count were repeated, it would fall into the normal range for the particular eye. Occasionally, when a count was made over an area containing a pathologic condition, there would be a significant drop. But when the count was repeated, it would fall into the general pattern of the count over this area.

These facts led us to postulate the idea of "repeatability," thereby enabling us to discard an occasional count which did not fall into the general pattern of the area.

The results of these studies show that intraocular neoplasms will concentrate P^{32}, as previously demonstrated by Thomas and his co-workers.[8] This concentration can be detected if the tumor is located in the anterior half of the globe. Improvement of instrumentation will probably allow greater accuracy in localizing a posterior-segment lesion with this method.

TABLE 2.—*Analysis of Redding of P^{32} Concentration on Forty-Nine Cases*

Case No.	Diagnosis	Average Count per Minute, Normal Eye	High Count per Minute		Variation from Average (Normal Eye), %	
			Normal Eye	Pathologic Eye	Normal Eye	Pathologic Eye
1	Malignant melanoma of iris *	...	...	240	....	35% †
2	Serous detachment	207	236	265	14%	23%
3	Anterior and posterior uveitis	145	176	186	21%	29%
4	Serous detachment	180	219	213	21%	18%
5	Malignant melanoma *	228	260	369	15%	61%
6	Malignant melanoma *	112	138	118	12%	5%
7	Uveitis and retinal detachments	158	183	236	16%	49%
8	Serous detachment	295	334	315	13%	7%
9	Serous detachment	218	242	269	11%	22%
10	Large nevus (benign)	215	257	273	20%	27%
11	Malignant melanoma with vitreous hemorrhage *	198	200	465	1%	135%
12	Tumor of iris (benign)	106	125	125	18%	18%
13	Malignant melanoma *	209	219	275	4%	32%
14	Inflammatory anterior uveitis with keratitis (possible ring melanoma of ciliary body)	226	247	368	10%	62%
15	Malignant melanoma (?)	130	147	153	13%	18% ‡
16	Malignant melanoma *	118	131	198	11%	68%
17	Metastatic lesion from carcinoma of breast	139	...	O.D.: 304 O.S.: 291	....	120% § 110%
18	Serous detachment	234	256	264	10%	13%
19	Malignant melanoma *	225	245	218	10%	— 3%
20	Posterior chorioretinitis	262	313	388	23%	48%
21	Anterior chorioretinitis	284	318	447	12%	57%
22	Phthisis bulbi *	186	212	246	14%	32%
23	Melanoma of disc	225	285	292	26%	29%
24	Serous detachment	266	277	267	3%	0%
25	Malignant melanoma of macula *	149	170	207	14%	39%
26	Malignant melanoma *	290	309	440	7%	55%
27	Choroidal hemorrhage	261	299	330	23%	26%
28	Absolute glaucoma	152	...	179	....	17% ‡
29	Metastatic carcinoma	235	272	370	15%	58%
30	Choroidal hemorrhage	234	298	243	27%	4%
31	Malignant melanoma of ciliary body *	322	...	455	....	41% †
32	Retinal detachment	277	350	287	26%	4%
33	Malignant melanoma of ciliary body *	364	421	569	15%	60%
34	Acute exudative choroiditis with solid detachment, due to inflammation *	442	498	614	12%	38%
35	Malignant melanoma *	187	190	397	1%	111%
36	Malignant melanoma *	218	252	400	15%	83%
37	Serous detachment	209	235	236	18%	18%
38	Serous detachment	356	381	445	7%	24%
39	Vitreous hemorrhage	210	246	249	12%	14%
40	Malignant melanoma *	248	294	365	19%	53%
41	Malignant melanoma *	406	440	587	9%	44%
42	Malignant melanoma *	191	203	390	6%	100%
43	Staphyloma of globe *	146	154	179	5%	22%
44	Uveitis with traumatic vitreous hemorrhages	179	202	379	13%	111%
45 46 47	Not included, as no report available to date; eyes enucleated					
48	Uveitis	118	134	153	14%	29%
49	Malignant melanoma (?)	132	158	225	19%	70% ‖
50	Choroidal hemorrhage due to degeneration	141	165	153	17%	5%
51	Choroidal hemorrhage	210	235	249	7%	18%
52	Melanoma of limbus (benign)	132	147	132	11%	0%

All our readings were analyzed on a statistical basis, determining the standard deviation (σ) in the normal eye by the formula:

$$\sigma = \left[\Sigma_X^r \, {}^1/_N \, (X - X_1)^2 \right]^{1/2}$$

The reading in the pathologic eye was considered significant only if it varied from the average in the normal eye by 3 or more σ.

* Eye enucleated—diagnosis established by histopathologic report.

† Only eye; so count was compared with that for the healthy sclera.

‡ A different technique in counting was used; therefore comparable data are not available.

§ Bilateral metastatic lesion; count compared with that for lobe of ear.

‖ Eye not enucleated, as there is some clinical doubt as to whether or not we are dealing with a malignant growth.

Serous detachments, hemorrhages in the vitreous, and choroidal hemorrhages without clinical signs of inflammation fail to concentrate P^{32}, but inflammatory and phthisical eyes produce an increased concentration of radioactive phosphorus. Thus, this test will be of value in detecting intraocular tumors if the latter two possibilities can be excluded by clinical means.

It must be stressed, therefore, that radioactive P^{32} is a test and that it should be used in conjunction with, and should not replace, other diagnostic methods, clinical judgment, and experience.

SUMMARY

1. The variations in concentration in the normal eye may run as high as 28% from the arithmetic mean, though generally the variation is less than 20%.

2. A variation of 30% or more should be considered a significant concentration of P^{32}.

3. Serous detachments and choroidal and vitreous hemorrhages without signs of inflammation show no significant concentration of P^{32}.

4. Inflammatory lesions, if active, will show a significant concentration of P^{32}.

5. Neoplasms in the posterior segment of the globe may or may not show a significant concentration of P^{32}, depending on their size, activity, and location.

6. Neoplasms in the anterior segment of the globe show a significant detectable concentration of P^{32}.

2117 Spruce St.

REFERENCES

1. Silverstone, B.; Sweet, W. H., and Robinson, C. V.: Clinical Use of Radioactive Phosphorus in Surgery of Brain Tumors, Ann. Surg. **130**:643-650 (Oct.) 1949.

2. Moore, G. E.: Radioactive Diiodofluorescein in Diagnosis and Localization of Brain Tumors, Science **107**:569-571 (May 28) 1948.

3. Marshak, A.: Uptake of Radioactive Phosphorus by Nuclei of Liver and Tumors, Science **92**:460-461 (Nov. 15) 1940.

4. Kenney, J. M.; Marinelli, L. D., and Woodard, H. A.: Tracer Studies with Radioactive Phosphorus in Malignant Neoplastic Disease, Radiology **37**:683-687 (Dec.) 1941.

5. Marinelli, L D., and Goldschmidt, B.: Concentration of P^{32} in Some Superficial Tissue of Living Patients, Radiology **39**:454-463 (Oct.) 1942.

6. Low-Beer, B. V. A.; Bell, H. G.; McCorkle, H. J., and Stone, R. S.: Measurement of Radio-Active Phosphorus in Breast Tumors in Situ; a Possible Diagnostic Procedure, Radiology **47**:492-493 (Nov.) 1946.

7. International Commission on Radiologic Protection, London, July, 1950.

8. Thomas, C. I.; Krohmer, J. S., and Storaasli, J. P.: Detection of Intraocular Tumors with Radioactive Phosphorus, A. M. A. Arch. Ophth. **47**:276-286 (March) 1952.

EFFECT OF CIGARETTE SMOKING ON FLICKER FUSION THRESHOLD

Clinical Observations on Normal Smokers and Nonsmokers

LAWRENCE L. GARNER, M.D.
E. FRANKLIN CARL, M.D.
AND
ERWIN E. GROSSMAN, M.D.
MILWAUKEE

THE FUSION frequency of flicker is that state of successive light stimuli which appear to the eye to be a continuous light and free from any flickering sensation. It depends upon chronaxie, latent period, refractory period of the retina, visual pathways, and visual centers and as a result may indicate the excitability or depression of the visual system, and perhaps of the entire central nervous system. Flicker frequency fusion has no correlation with the visual acuity and depends probably on a visual sensation not at all related to the acuity of vision. A Maddox rod of clear color and large diameter placed before the eye reduced the visual acuity to a minimum; yet the flicker fusion frequency was not affected.

While visual acuity depends upon the ability of the eye to resolve two separate stimuli separated in space, flicker perception depends upon the ability of the eye to resolve two stimuli separated by time.

Although flicker fusion has been employed by visual physiologists for many years, the technique for routine clinical investigation has been adapted only recently, and a variety of investigators upon analysis have revealed that flicker fusion is directly related to the vascular supply of the retina or brain. The detailed physiology of flicker fusion has been studied in recent years by Hecht,[1] and an investigation of the literature reveals that flicker fusion frequency has been found influenced by fatigue,[2] age,[3] alcoholism,[4] hypothyroidism,[5] anoxia,[6] anxiety,[7] and the use of drugs, such as testosterone [8] and amphetamine.[9] Krasno and Ivy [10] describe its clinical use and aid in the diagnosis, therapy, and prognosis of heart disease; Young [11] employed the flicker fusion test in the first Columbia-Greystone Brain Research Project and found that under certain conditions the return of mental health following psychosurgery was associated with changes in the flicker fusion, and Larson [12] described the effect of smoking on the fusion frequency of flicker in 20 subjects, finding that with abstinence the first cigarette smoked caused an immediate rise in the fusion frequency of flicker and that with subsequent smoking this might become reduced. The mechanism for this dual effect is not understood. Fabricant and Rose [13] recently published their findings, employing 50 subjects. They observed an immediate rise

Read before the Chicago Ophthalmological Society, Oct. 6, 1952.

From the Department of Ophthalmology, Milwaukee County Hospital, Milwaukee County Dispensary, and the Marquette University School of Medicine.

in the fusion frequency of flicker in 40 subjects after smoking cigarettes and a decrease in the fusion frequency in the remaining 10. In the field of ophthalmology, flicker fusion frequency has been used as an office procedure by Weekers for the past eight years and by Miles for the past five years. Miles [14] employed flicker fusion frequency for testing the entire visual field in both normal and abnormal ophthalmological conditions. In amblyopia ex anopsia [15] he found the central area reacting or performing like the peripheral retina in that a higher flicker fusion frequency was noted. Weekers [16] reported the early depression of the flicker fusion frequency field in glaucoma. A personal communication reveals that Krasno finds that smoking causes an abnormal flicker fusion glyceryl trinitrate (nitroglycerine) test in some subjects and that when these people refrain from smoking the test becomes normal. In the normal subject glyceryl trinitrate results in a decrease in the flicker fusion frequency. An abnormal glyceryl trinitrate flicker fusion test indicates that the flicker fusion threshold value has decreased or sensitivity has improved following the use of this drug.

Since smoking can, for practical purposes, be considered almost a normal function of the adult population, our interest in ascertaining the effects of smoking on the flicker fusion frequency of 96 healthy student nurses in an age group of 18 to 23 years was elicited. Twelve additional subjects were employed, ranging in age from 24 to 53 years, with an average age of 36.6 years. Of the total number of subjects under observation, all were women except for two men residents in ophthalmology.

The instrument employed for testing fusion frequency of flicker was devised and described by Krasno and Ivy [10] and consists of a 6-volt tungsten lamp which is encased in a metallic cylinder containing a rectangular window, so that light is on one-half of the time when the cylinder rotates. The speed of rotation is controlled by a motor and frequency oscillator. When low-speed rotation is employed, a very coarse flicker is noted; and as the speed of rotation is increased, the frequency increases and the flicker becomes finer, and eventually disappears at a certain endpoint (fusion). The subject has only to state whether flicker sensation is or is not noted, and since the fusion frequency of flicker is not an index of the visual acuity, it makes no difference whether corrective lenses are or are not worn by the subject.

PRESENT INVESTIGATION

The present study consisted in observing the effect of cigarette smoking on the flicker fusion threshold of a group of 108 apparently healthy adults. Of the total number of subjects, 55 were smokers and 53 were nonsmokers. The student-nurse smokers in this group smoked from 3 to 25 cigarettes daily and had been smoking for two weeks to four years, whereas the graduate nurses, being older, had a longer history of smoking. The two male subjects were both nonsmokers.

In the smoker group, a period of abstinence from smoking for at least 10 to 12 hours was observed by the subject at any time prior to the flicker determination. All testing was performed between the hours of 9:30 a. m. and 4:00 p. m. The waiting room was necessarily separated from the smoking and testing rooms, inasmuch as errors and confusing results were noted if the subject was permitted to sit in a poorly ventilated room containing cigarette smoke while awaiting her preliminary readings. The smoking room was well ventilated, but when testing for the effect of denicotinized cigarettes it was found best that the subject be placed in a ventilated room where no smoking had been done with ordinary cigarettes.

All cigarettes employed were furnished by the examiners, and consisted of such popular brands as Camel, Chesterfield, Embassy, Lucky Strike, Old Gold, Pall Mall, and Phillip Morris. They had been purchased on the open market, and no attempt was made to influence the subject's choice of cigarette. When denicotinized cigarettes were employed, the Sano brand was furnished.

The method employed in testing the subjects was essentially that described by Krasno and Ivy [10] in their original report describing the use of their flicker photometer. Standard conditions of surrounding illumination, visual angle, exposure, and illumination of the test patch were observed from test to test, and several trial readings were taken such that each subject was well acquainted with the routine of examination. Binocular foveal fixation was employed at a distance of 60 in. (1.5 meters). After this, 5 to 8 readings were taken, and additional readings, for a total of 10, were taken, if a base line reading was not easily obtained. These readings were recorded and then averaged to obtain the subject's flicker fusion threshold before smoking. To facilitate study, the flicker rate was reduced to flashes per second rather than to flashes per minute. The postsmoking flicker fusion rate was averaged, but in the groups that presented rise or fall of the flicker fusion frequency, the averages were made by taking those readings immediately after smoking, up to and inclusive of the reading which revealed that the flicker fusion rate had returned to the presmoking base level. The postsmoking readings were taken immediately after smoking and repeated approximately 1, 2, 3, 5, 7, 9, 11, 15, 20, 25, and 30 minutes thereafter. Each subject had a minimum of two tests made at intervals of at least seven days apart.

RESULTS

Of a total of 108 subjects, it became increasingly apparent that not all fall into a common pattern, and some interesting observations were noted. Because of the various types of results noted, it was decided to place the subjects in various groups depending upon their reactions to the tests. Thirty-five of the subjects revealed an increase in the flicker fusion frequency following smoking; 21 revealed a decrease; 40 presented no alterations in the flicker fusion frequency after smoking; 5 presented an initial rise followed by a secondary fall in the flicker fusion rate, and 7 subjects could not be considered good candidates because of the erratic results, as will be noted elsewhere. Because of the wide range of data noted, each subject was tested at least on two occasions at a minimum interval of seven days apart, and some of the subjects had as many as four separate tests made. An analysis of the separate groups is presented in Table 1.

1. *Initial Rise Group* (Chart 1).—On a total of 35 subjects in this group, 88 separate tests were conducted on days ranging from seven days to six weeks after the initial tests had been performed. Of this group, 20 were smokers and 15 were nonsmokers. Considerable variations were noted occasionally in the same patient, and an increase of 0.6 flash per second was considered significant. In this group the flicker fusion threshold returned to the predetermined base line within one to eight minutes, the majority finding their base level flicker fusion rate within three minutes. Of this group of 35 subjects, 8 were given a second cigarette after the base line had been reached and 10 additional minutes had elapsed. In each of these eight subjects a rise in the flicker fusion frequency was again noted, but it was essentially somewhat lower than the first, by 0.1 to 0.2 flash per second. Eight subjects in this group were given denicotinized cigarettes after a flicker fusion threshold had been determined after an abstinence period, and no essential changes in the effect on flicker fusion frequency were noted, indicating that the rise could be eliminated by this means.

2. Initial Decrease Group (Chart 2).—This group consisted of 21 of the subjects tested, and a total of 69 individual tests were performed, with a minimum of 2 tests per subject. Of this group, 10 were smokers and 11 were nonsmokers. The decrease in number of flashes following the smoking of one cigarette ranged from 0.5 to 2.1 flashes per second. The presmoking flicker fusion threshold base line

TABLE 1.—*Analysis of Group*

	Subjects	No. of Tests	Unsatisfactory Tests	Smokers	Non Smokers	Nausea, Etc.
Initial rise	35	78	6	20	15	0
Initial drop	21	69	2	10	11	3
No effect	40	82	4	22	18	2
Poor candidate	7	18	18	1	6	3
Rise and fall	5	13	0	3	2	0
Total	108	260	30	56	52	8

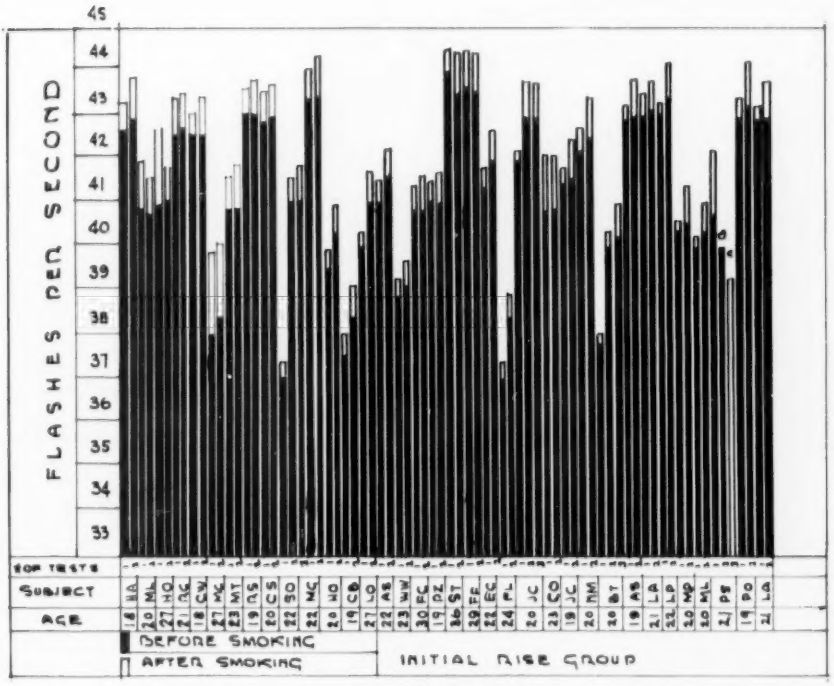


Chart 1.—Initial rise group.

showed an increase in 14 of the subjects when repeat tests were performed after the initial observation; a decrease was noted in 4 and no alteration in 3, of the subjects tested. The increase of flashes in the presmoking base flicker fusion frequency ranged from 0.05 to 1.2 flashes per second. Each subject in this group was given an additional test using a denicotinized cigarette, the nature of which was at times known and other times unknown to the subject. The results were dramatic

in that the presmoking and postsmoking readings were then practically identical (Chart 3). Of this group of 21 subjects, 14 presented no alteration in flicker fusion frequency after smoking one denicotinized cigarette; 6 subjects presented a decrease ranging from 0.05 to 0.2 flash per second, and 1 subject showed a decrease of 0.3 flash per second. Three of the subjects in this group were tested by taking flicker fusion readings after permitting the subjects to sit in a smoke-filled room for five minutes, an initial flicker fusion threshold having been taken in a smoke-free room

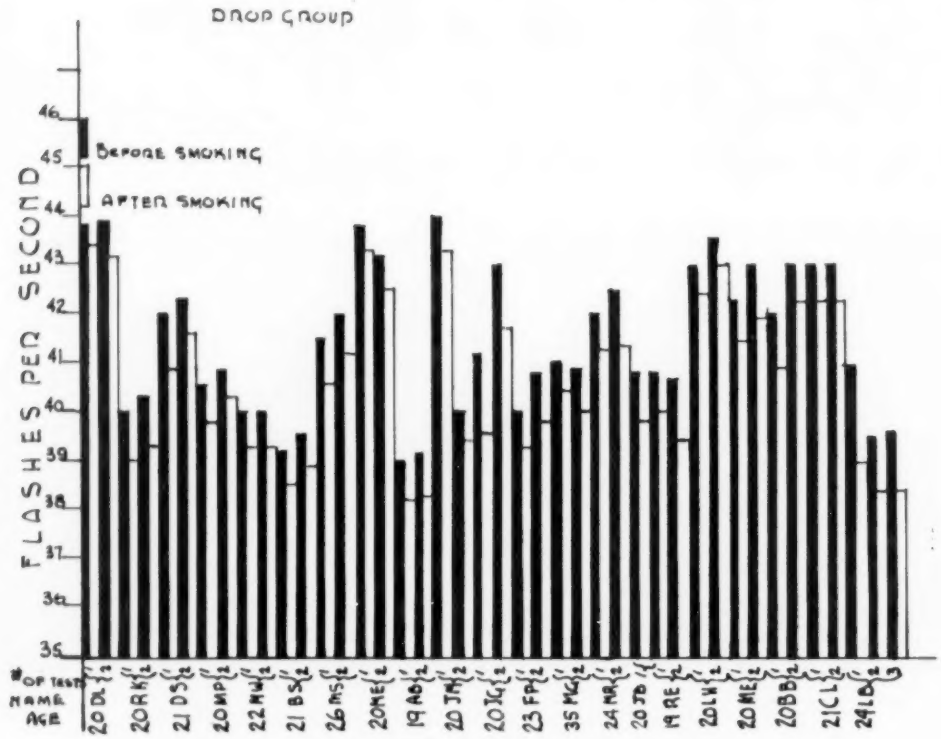


Chart 2.—Initial decrease group.

about 10 to 15 minutes prior to this. In each instance the inhalation of smoke produced results almost identical to those noted after smoking, and the drop in flicker fusion ranged from 0.7 to 1.2 flashes per second. Two of the subjects were permitted to smoke a denicotinized cigarette in a nonventilated room that had been used for smoking; again, the results were similar to those that followed smoking the ordinary cigarette, and a drop in flicker fusion of 0.6 flash per second and upward was noted within one minute after the subject was removed from the smoke-filled room. Two subjects were given glyceryl trinitrate tablets, 1/100 grain (0.6 mg.), sublingually immediately after the first postsmoking reading was taken, and a prompt return to the base line, and slightly above, was noted. Three subjects in this group complained of headache, vertigo, faintness, coldness of the extremities, or clammy hands. Of these three subjects, two were nonsmokers and one smoked two to three cigarettes

per day. The latter admitted that she always felt "sick" for about one hour after smoking but continued to smoke "because everybody else did." In all 21 subjects the decrease in flicker fusion frequency occurred immediately after smoking or being subjected to smoke, and the recovery time for return to the presmoking base line in most of the subjects varied from within 4 to 6 minutes, although several took from 14 to 50 minutes. The subject, L. B., a graduate nurse of 24, presented the most striking results in that sudden decrease in flicker fusion frequency and

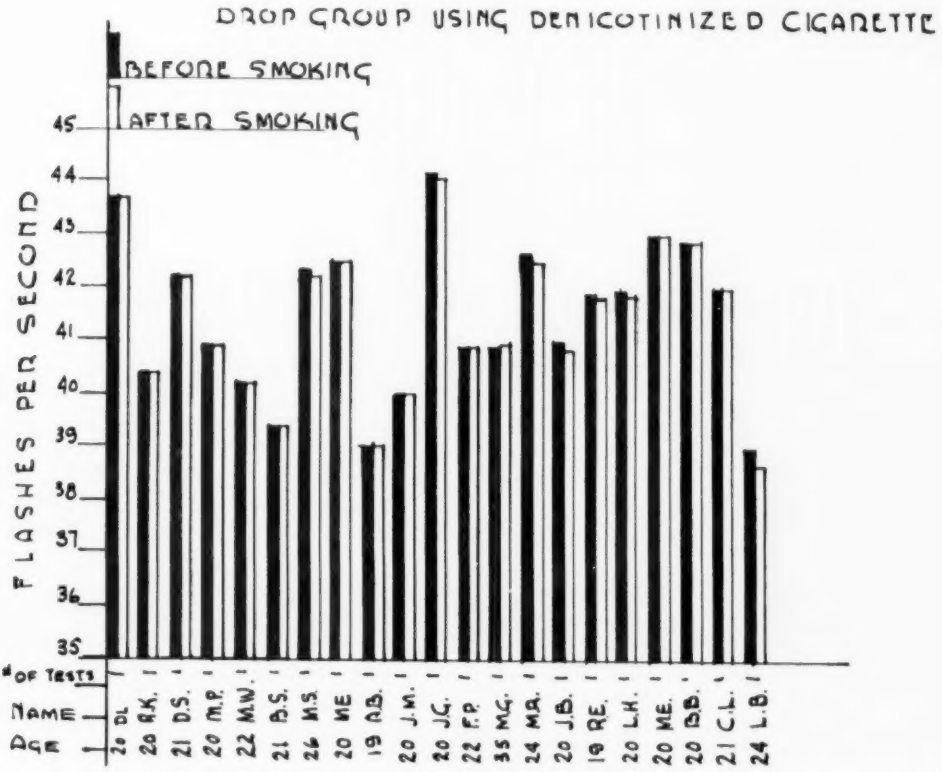


Chart 3.—Decrease group using a denicotinized cigarette.

prolonged recovery time followed the smoking of one cigarette. The subject's hands were warm and dry prior to smoking and became cold and clammy shortly after smoking, along with a subjective sense of ill-being. Forty to 60 minutes was required for return to her presmoking subjective sense of well-being. The use of 1 tablet of papaverine hydrochloride, 1½ grains (0.1 gm.), orally reduced this recovery time of subjective well-being to about 20 minutes following smoking. The return to flicker fusion base threshold was expedited by this means, and about one-half the time was required. The return to base threshold following the use of papaverine in this instance coincided with her return to a feeling of well-being. Fundus

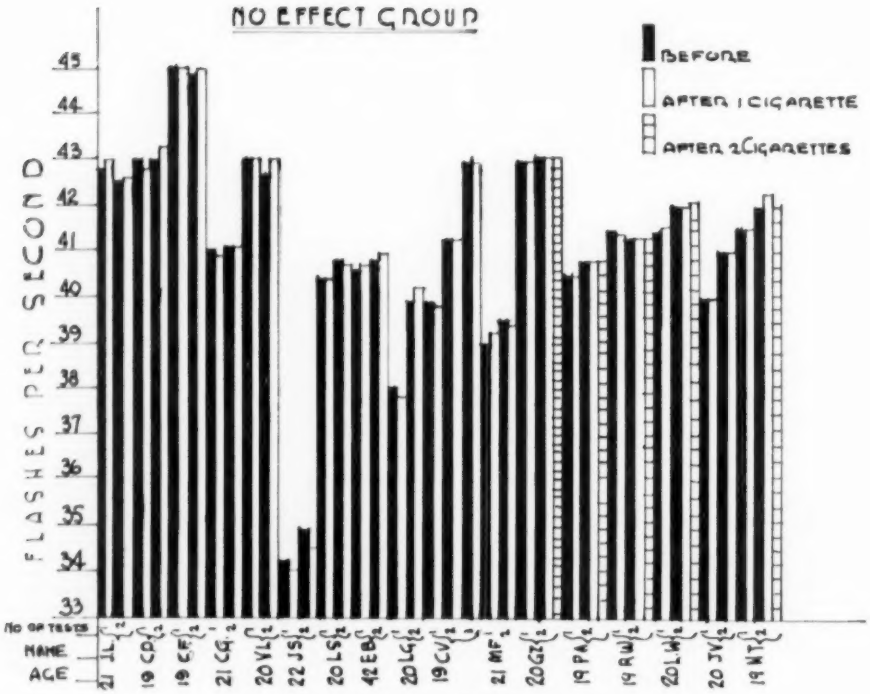


Chart 4.—No effect group.

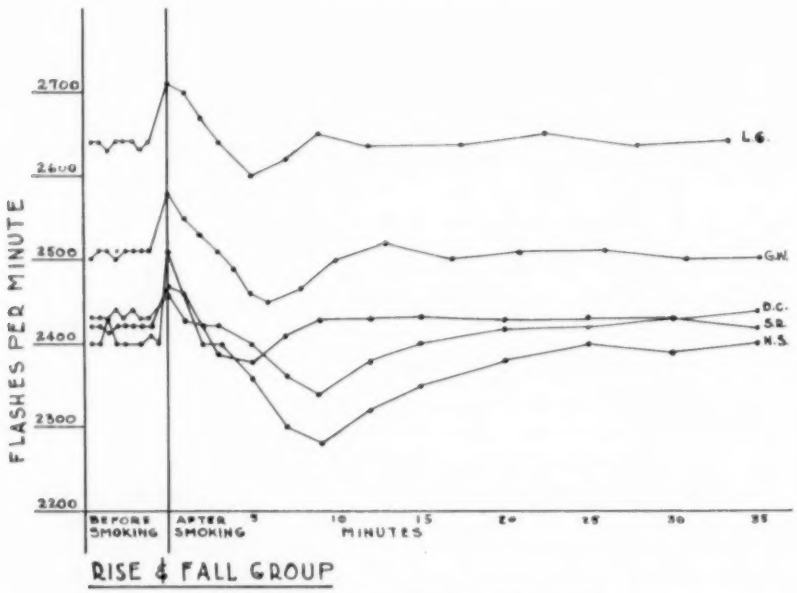


Chart 5.—Threshold rise and fall group.

examinations on this group failed to reveal any gross evidence of vascular spasm on routine ophthalmic examination despite the pronounced effect subjectively and objectively after smoking.

3. *No Effect Group* (Chart 4).—This group consisted of 40 of the original 108 subjects, and a total of 82 separate tests were conducted, on separate days. Of these 40 subjects, 22 were smokers and 18 were nonsmokers. Any subject with a rise or fall of 40 flashes per minute or less was considered a candidate for this group and the test repeated. Twenty subjects in this group were given a second cigarette within 15 to 30 minutes after completion of their first postsmoking readings; in all the subjects there was no pertinent change noted, and the readings were essen-

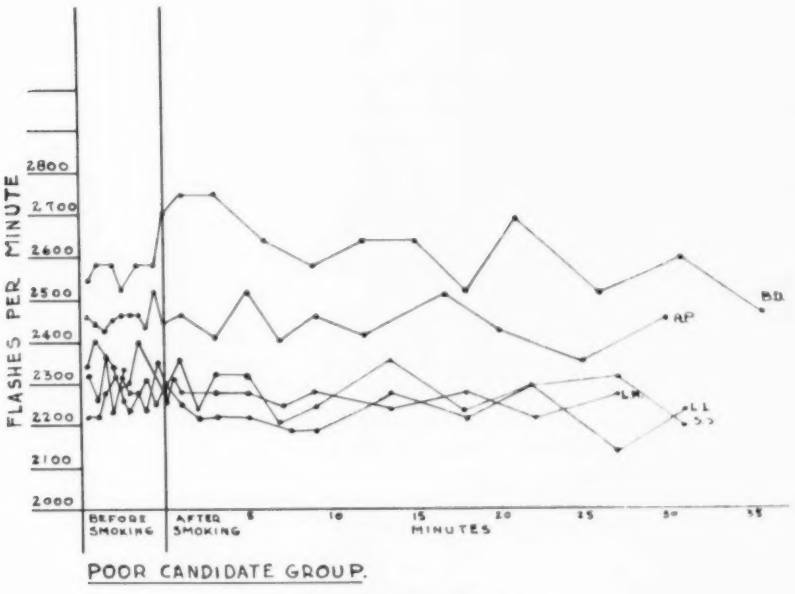


Chart 6.—Poor candidate group.

tially as noted after the first cigarette. Two of the subjects in this group noted nausea, faintness, and some vertigo; both were nonsmokers.

4. *Threshold Rise and Fall Group.*—This consisted of five subjects, of whom three were smokers and two nonsmokers, the common characteristic of this group being the sharp rise immediately after smoking, with return to base line within two to four minutes, followed by a secondary drop in the flicker fusion threshold and again a return to the base line, the latter return being somewhat slower, as noted in Chart 5.

5. *Poor Candidate Group.*—This group consisted of seven subjects, of whom six were nonsmokers. A total of 18 separate tests were performed here, and in 4 of the subjects it was impossible to obtain any uniformity in the presmoking individual flicker fusion base line during the initial testings. Subsequent tests failed to produce any improvement, and the presmoking readings could be considered as

erratic as the postsmoking readings which were taken in two of the subjects. In the remaining three subjects the presmoking flicker fusion threshold base line was somewhat less erratic but became more so after smoking. Chart 6 reveals this erratic

TABLE 2.—*Effect of Smoking on the Flicker Fusion Threshold of Fifty-Four Smokers and Forty-Six Nonsmokers**

Group	No. of Persons (P)	No. of Observations (N)	Before			After		
			Range (R)	S.D. (v_x)	Variance (v^2_x)	Range (R)	S.D. (v_x)	Variance (v^2_x)
Smokers								
A	19	114	36.26	13.91	193.49	94.21	37.18	1,382.35
B	22	132	10.00	3.95	15.60	15.00	5.92	35.05
C	3	18	10.00	3.95	15.60	66.67	26.31	692.22
D	10	60	23.00	9.81	96.24	95.00	37.49	1,405.50
Sum	54	324	21.30	8.41	70.73	60.56	23.90	571.21
Nonsmokers								
A	15	90	30.00	11.84	140.19	61.33	24.20	585.64
B	18	108	7.78	3.07	9.42	27.22	10.74	115.35
C	2	12	20.00	7.90	62.41	165.00	65.11	4,239.31
D	11	66	9.09	3.59	12.89	81.82	32.29	1,042.64
Sum	46	276	15.87	6.26	39.19	57.39	22.65	513.02
Total: Smokers and Nonsmokers								
A	34	204	32.94	13.00	169.00	79.71	31.46	989.73
B	40	240	9.00	3.55	12.60	20.50	8.09	65.45
C	5	30	14.00	5.52	30.47	106.00	41.83	1,749.75
D	21	126	57.14	22.55	508.50	88.10	34.77	1,208.95
Total	100	600	18.80	7.42	55.06	59.10	23.32	543.82

* Average ranges, standard deviations and variances from individual means (first experiment).

TABLE 3.—*Effect of Smoking on the Flicker Fusion Threshold of Fifty-Four Smokers and Forty-Six Nonsmokers**

Group	No. of Persons (P)	No. of Observations (N)	Before		After	
			Mean	S.E.	Mean	S.E.
Smokers						
A. Initial rise	19	91	2,435.6	10.2	2,479.7	11.7
D. Initial drop	10	51	2,493.0	7.5	2,417.3	11.2
Nonsmokers						
A. Initial rise	15	52	2,420.0	13.2	2,503.4	12.9
D. Initial drop	11	48	2,470.4	8.1	2,412.5	10.3
Total: Smokers and Nonsmokers						
A. Initial rise	34	143	2,429.9	8.0	2,490.2	8.4
D. Initial drop	21	99	2,482.1	5.5	2,414.9	7.6
B. No effect	40	240	2,500.6	7.0	2,502.0	7.8
C. Rise and fall	5	30	2,462.7	19.8	2,464.4	22.0

* Grand means and standard errors of these means prepared by J. V. Talacko, S.D., Assistant Professor of Mathematics, Marquette University, Milwaukee.

nature in five of the subjects of this group on whom readings were taken before and after smoking. Two of the subjects in this group, both nonsmokers, produced the most violent reactions after the smoking of one cigarette. They were the two oldest subjects of the entire group of 108 and were aged 46 and 53, respectively. Both noted considerable nausea and emesis, one occurring 6 minutes after smoking and

the other 28 minutes after smoking. Subject L. L. noted vertigo immediately after smoking, with emesis 28 minutes later, associated with considerable hysteria and emotional instability. Further testing here was not considered, for obvious reasons. Subject L. M., aged 46, noted nausea, weakness, and clammy perspiration after smoking but was still cooperative after emesis. An attempt was made to repeat the test in this instance at a later date, but since no satisfactory flicker fusion base line could be obtained at the second attempt, the testing was not concluded. Of the remaining five subjects in this group, one noted moderate nausea and vertigo, which subsided within 10 minutes after smoking. This subject was also a nonsmoker.

For purposes of statistical analysis, the services of Joseph V. Talacko, S. D., assistant professor of mathematics, Marquette University, Milwaukee, were retained, and his computation of statistics is shown in Tables 2 and 3.

Because of the variability of flicker fusion threshold from subject to subject and the presence of variance from person to person in relation to the variance due to the effect of smoking, Dr. Talacko has preferred to employ the Fisher *f*-test in the group analysis here. Variability may be measured by range, standard deviation, standard error, or variance. In this study variance was used as the statistical yardstick. The term "variance" as employed here is a statistical one which measures the dispersion of a statistical distribution and has a totally different meaning from the word "variability," as used to indicate changes.

COMMENT

It appears that smoking affects the variance of all subjects but that a marked degree of variance is noted in the smoker, in contrast to the nonsmoker. It would seem that one is able to discriminate groups of smokers from nonsmokers by study of the variance prior to smoking, but once a cigarette is smoked this difference in variance ratio is lost. This discrimination does not hold up as well when the subjects are divided into arbitrary groups.

On the basis of these findings, we note a statistically significant degree of variance between smokers and nonsmokers before smoking, between smokers before and after smoking, and between nonsmokers before and after smoking, but not between smokers and nonsmokers after smoking.

It has long been accepted that smoking produces variable degrees of vasoconstriction, particularly of the peripheral vascular tree, and that this in itself is not harmful to the normal person. Kusick and Herrell [17] described their retinal findings in five patients who were known to have an idiosyncrasy to tobacco, employing a modified Morgan graticule in a Keeler ophthalmoscope. In each of these five hypersensitive subjects a measurable reduction in arteriolar caliber, although of short duration, was noted after smoking. This reduction in size of vessels averaged about 20.8%. In our series ordinary ophthalmoscopic examination was made, employing the Morton or May head ophthalmoscope, and in no instance was any evidence of local or general spasm or visible degree of vasoconstriction noted. It is obvious from this observation that the latter method is not adequate for study of vascular changes in the retina following the act of smoking.

That nicotine is the etiological factor in the decrease in flicker fusion frequency after smoking becomes easily apparent when observations are made in the case of ordinary and denicotinized cigarettes. In each instance the decrease could be

avoided, or almost completely avoided, if a denicotinized cigarette was substituted for the ordinary type of cigarette. In the case of L. B., who presented the most profound evidence of reaction to nicotine, it is apparent that some effect was still persistent when the denicotinized cigarette was employed and a decrease of 0.3 flicker per second was registered, but the return to normal was definitely not as delayed. Apparently the amount of nicotine still present even in a denicotinized cigarette is sufficient to produce this effect in a subject who presents a marked degree of hyperreactibility to nicotine. The question as to whether nicotine is more toxic for some than for others arises in view of the above observation, and will bear further investigation. That there is a decided degree of effect in some subjects, in contrast to others, insofar as decrease in flicker frequency of fusion threshold is concerned must be considered here as evidence of increased sensitivity or hyperirritability to nicotine in these subjects.

The effects of the vasodilators, although employed in isolated cases, indicated the reversible nature of the effect of smoking, as well as its mechanism.

TABLE 4.—*Reversal of Nicotine Effect by Glyceryl Trinitrate (Nitroglycerine)**

Case No.	Field	After 1 Cigarette			After Glycol Trinitrate, 1/150 Grain		
		Center	Peripheral	Disc †	Center	Peripheral	Disc
1	Normal	−3	0	−2.5	....	....	Not taken
2	Normal	−3	−2	−2	+1	+2	+3
3	Low peripheral and near disc	−2	0	−2	+3	+4	+5
4	Normal	0	−3	−5	+3	+2	+2
5	Low	+2	−1	−8	+4	+3	+2
6	Normal	−5	−3	−5	+1	+3	+4
	Average	−2	−1.5	−4	+2	+2	+4

* Data furnished by Dr. Paul W. Miles.
† Note advantage of taking fields in disc area.

In a recent personal communication, Miles enclosed some data (Table 4) which may show the tendency of a vasodilator to reverse the effects of cigarettes. Of even greater interest in the data furnished by Miles is the obvious significance of readings taken below and above the blind spot. In unpublished work which he reported to the Chicago Ophthalmological Society in 1951, Miles found that fusion frequency of flicker may decrease after one cigarette from 4 to 8 flashes per second if measured a few degrees above or below the blind spot. The subjects employed in his data were six postgraduate physicians, all normal, about age 28 except for Case 3, an obese person whose family background revealed multiple early cardiovascular deaths. Miles would call the latter a positive Krasno-Ivy test. One notes how much better it is to perform this test around the disc rather than by foveal fixation. The minus figures in his data mean that the flicker rate in the general part of the visual field indicated was that many flashes per second below the original field taken; the plus figures mean that many flashes higher. The "disc area" means an average of that above and below the disc.

Nurse L. B., who presented the most marked response to cigarette smoking, volunteered the information that since this work has been done she has had occasion to marry and as a result has now learned to enjoy an occasional cocktail or other drink before meals. She notes that she is now able to smoke a cigarette with only minimal subjective discomfort, or practically none, provided that she has a

drink or two prior to smoking. This can be corroborated by the flicker fusion frequency test and would seem to indicate a mechanism similar to that of the use of vasodilators.

The results observed in the subjects permitted to inhale smoke while seated in a smoke-filled room would suggest that smoking is in itself not required if the subject is exposed to a concentration of cigarette smoke in a nonventilated or poorly ventilated room. The latter information becomes important in the conduct of this type of investigation, and indicates that adequate ventilation and the use of separate rooms are required if one hopes to arrive at any accurate conclusions.

Despite the above precautions, we note in Table 1 that 12 primary tests were worthless, in addition to those performed upon the 7 subjects placed in the poor-candidate group. A definite degree of fluctuation or variation of results was noted in some of the subjects which is not indicated in the graphs. A small number of subjects would present a rise in the flicker fusion threshold after cigarette smoking at one time and subsequently present no effect when the test was repeated one or two times. Other subjects presented a fall in flicker fusion threshold after smoking which later could not be duplicated. The final results employed in these instances were those which could be duplicated; but, nevertheless, one was aware of the variables that occurred from time to time, resulting in a rule that no deductions be made from any single test. In our series, 12 of the subjects presented a variability of findings of one type or another.

It is possible that these variations might be eliminated with the use of a flicker field instrument, since the more sensitive extramuscular region could thus be tested. There is a fundamental difference between the Ivy apparatus employed here and the stroboscopic apparatus, which may be of interest in future investigations which are being considered. The light-dark ratio of the Ivy instrument remains at 50:50 at different flicker frequencies, whereas the stroboscopic instrument has a flash duration of approximately 50 μsec. at all frequencies. A personal communication from Dr. Miles reveals, interestingly, his experience with the Krasno-Ivy instrument, which he found to be defective. He employed two of these instruments and found that they varied with temperature, as well as not being able to remain on the stated frequency. It is his belief that the General Radio Strobotac, or a modification of this type as built by any competent radio man, is a superior instrument.

An observation not shown in the graphs is the effect of sound stimuli on the results. In several instances the passing of a noisy cart in the hospital or an incident that produced a disturbing noise in the corridor produced a decided effect on the readings being taken. In every case a decided drop in the flicker fusion rate was noted, the rate becoming erratic for one to three minutes thereafter, after which the subject retained a level very near the last reading prior to the disturbance. In these cases the tests were repeated at later intervals. This disturbing effect of sound upon the efficiency of the patient was so pronounced that the conduction of tests was moved to another portion of the building and extrinsic sounds kept at a minimum.

The two subjects in this group in whom unexpected nausea and emesis resulted were both well above the average age of this group as a whole. It is possible that the approach of the menopause, with its associated emotional instability, may have been a factor here, and this factor should merit consideration in future investigations.

The future findings of additional investigations dealing with a smaller group of subjects, but with a far greater number of individual tests employing standard conditions for each test over a prolonged period of observation, may be a means of ascertaining the possibility of such a thing as a normal flicker fusion threshold range. It may also offer the means of eliminating or diminishing the variability in threshold rates noted in this series.

SUMMARY AND CONCLUSIONS

Cigarettes had an effect of raising the flicker fusion frequency in 35 subjects and of lowering it in 21 subjects out of a total of 108 subjects tested.

Some subjects showed an extreme sensitivity to cigarettes in the flicker tests, while others revealed very little change. Those whose flicker fusion frequency was reduced by smoking showed an increase to the original level after glyceryl trinitrate (nitroglycerin), an apparent relief from vasoconstriction anoxia. It was found that the flicker test is sensitive enough to detect the small amount of nicotine found in denicotinized cigarettes. Furthermore, it was noted that subjects can absorb enough nicotine by sitting in a smoke-filled room to affect the flicker fusion frequency. The preliminary results as presented here would seem to indicate that regular smokers have a higher degree of variance than do nonsmokers. Thus, the measure of the flicker fusion threshold response may be potentially useful as a practical means of detecting the hyperreactors to nicotine. This information may become of some value to the clinician.

It is our opinion that among the factors that contributed to our inability to obtain consistent data in this study were (1) the mechanical imperfections of the Krasno-Ivy apparatus and (2) the technique of the Krasno-Ivy method of testing. There is no doubt, however, that the flicker test offers a fertile field for further research and continued study.

Miss Evelyn Mercer, R.N., Director of Nursing at the Milwaukee County Hospital, and Mrs. Lorraine Wempner, R.N., at the Milwaukee County Dispensary, gave aid and cooperated in this study. Dr. Paul W. Miles aided in the preparation of the paper.

REFERENCES

1. Hecht, S.: Bull. New York Acad. Med. **14**:21-45 (Jan.) 1938.

2. Simonson, E.; Enzer, N., and Benton, R. W.: Influence of Muscular Work on the State of the Central Nervous System, J. Lab. & Clin. Med. **28**:1555-1567 (Oct.) 1943.

3. Simonson, E.; Enzer, N., and Blankstein, S. D.: Effect of Age on the Flicker Frequency, J. Exper. Psychol. **29**:252-255 (Sept.) 1941.

4. Enzer, N.; Simonson, E., and Ballard, G.: Effects of Small Doses of Alcohol on the Central Nervous System, Am. J. Clin. Path. **14**:333-341 (June) 1944.

5. Enzer, N.; Simonson, E., and Blankstein, S.: State of Sensory and Motor Centers in Patients with Hypothyroidism, Ann. Int. Med. **15**:659-665 (Oct.) 1941.

6. McFarland, R. A.; Halperin, M. H., and Niven, J.: Visual Thresholds as Index of Modification of Effects of Anoxia by Glucose, Am. J. Physiol. **144**:378-388 (Aug.) 1945.

7. Krugman, H. E.: Flicker Fusion Frequency As Function of Anxiety Reaction: Exploratory Study, Psychosom. Med. **9**:269-272 (July-Aug.) 1947.

8. Simonson, E.; Kearns, W. M., and Enzer, N.: Effects of Oral Administration of Methyl Testosterone on Fatigue in Eunuchoids and Castrates, Endocrinology **28**:506-512 (March) 1941.

9. Simonson, E.; Enzer, N., and Blankstein, S.: Effect of Amphetamine on Fatigue of Central Nervous System, War Med. **1**:690-695 (Sept.) 1941.

10. Krasno, L. R., and Ivy, A. C.: Response of the Flicker Fusion Threshold to Nitroglycerin and Its Potential Value in the Diagnosis, Prognosis and Therapy of Subclinical and Clinical Cardiovascular Disease, Circulation **1**:1267-1276 (June) 1950.

11. Young, K., in Mettler, F. A., Editor: Selective Partial Ablation of the Frontal Cortex: A Correlative Study of Its Effects on Human Psychotic Subjects, The Columbia-Greystone Associates, New York, Paul B. Hoeber, Inc., 1949, Vol. 1, p. 257.

12. Larson, P. S.; Finnegan, J. K., and Haag, H. B.: Observations on the Effect of Cigarette Smoking on the Fusion Frequency of Flicker, J. Clin. Invest. **29**:483-489 (April) 1950.

13. Fabricant, N. D., and Rose, I. W.: Effect of Cigarette Smoking on the Flicker Fusion Threshold of Normal Persons, Eye, Ear, Nose & Throat Month. **30**:541-543 (Oct.) 1951.

14. Miles, P. W.: Flicker Fusion Frequency in Amblyopia ex Anopsia, Am. J. Ophth. **32**:225-231 (June, Pt. 2) 1949.

15. Miles, P. W.: Flicker Fusion Fields, Am. J. Ophth. **33**:1069-1076 (July) 1950.

16. Weekers, R.: L'exploration des fonctions visuelles en clinique par la mesure de la fréquence critique de fusion, Bull. et mém. Soc. franç. opht. **60**:331, 1947.

MALIGNANT MELANOMA OF THE IRIS AND CILIARY BODY OF A ONE-EYED PATIENT

Case Observed for Twenty Years

IVAN J. KOENIG, M.D.
BUFFALO

THERE have been a number of articles in the very recent literature dealing with various aspects of melanoma of the iris, ciliary body, and choroid. The histological background, as well as the discussion of the possible ectodermal origin of these tumors, has been minutely documented both in the journals and by Reese in his excellent book on "Tumors of the Eye." [1]

I present the following case because it has several unusual aspects, and because it had been under my personal observation for 20 years, though in all probability the entire cycle of the melanoma covered a span of some 50 years. I have not been able to find in the literature a case of melanoma of the iris with survival for this length of time. One's individual experience with such tumors is of necessity limited. Spaeth [2] saw only four malignant melanomas of the iris and ciliary body in his series of 170 ocular tumors studied over a period of 10 years. Therefore I hope that the presentation of this case will add to the cumulative experience of the unpredictable behavior of these neoplasms.

REPORT OF CASE

Mrs. M. L. D., aged 57, first consulted me on May 18, 1932. She stated she had noticed that the "black spot" in her right eye just below the pupil had been increasing in size. The change in size had been noticed for the past three years. She had been unable to read for two years, and blurring of vision had been slowly progressive during the past four years. Her husband volunteered the information that even before their marriage, 32 years previous, he had noted a "black spot" on the iris of this eye, which had changed in appearance since that time. At a later date, further details were obtained from two of her previous ophthalmologists, one of whom stated that he had observed an elevated mass, with noticeable vascularization, in the iris of this eye seven or eight years prior to my original examination. This was the patient's only eye. The left eye had been enucleated three years before her first visit to me. I was unable to obtain a pathological diagnosis from the left eye because the ophthalmologist who performed the enucleation went abroad and did not return. The family and other ophthalmologists who saw the case have assured me that there was no tumor present in the left eye.

Examination of the right eye revealed a nodule of the iris measuring 4.5 mm. in diameter, extending from the limbal area to the pupillary border. This mass was located in the 5 o'clock position. It was vascularized on the surface and appeared pigmented at its base. It seemed to be more or less thickened at its root and at this point was apparently in direct apposition with the posterior surface of the cornea. The adjacent chamber angle was completely filled by the mass. There was a posterior synechia in this quadrant, and there were some anterior cortical changes in the lens, as well as some sclerosis of the lens nucleus. The lens opacities accounted for the reduction of visual acuity to 6/20 with and without correction. The intraocular tension was 15

Presented at Fifth Annual Wills Eye Hospital Conference, March 20, 1953.

mm. (Schiøtz) and did not rise with mydriatics. The tumor extended approximately 1 mm. beyond the pupillary border with the iris dilated. Despite the lens opacities the fundus could be carefully searched, and no other lesions were located. The patient was in good general health and showed no evidence of any metastasis, but there was a mild hypertension present.

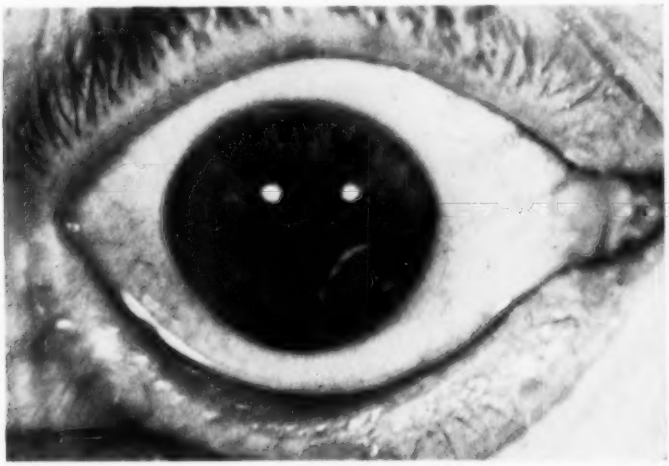


Fig. 1.—Clinical appearance of the tumor on May 18, 1932. Reproduced from Kodachrome.

Fig. 2.—Appearance of tumor Nov. 3, 1951, six years after cataract extraction. Reproduced from Kodachrome.

A tentative diagnosis of malignant melanoma of the iris was entertained and enucleation advised. The patient and family refused the removal of her only eye. After consultation, x-ray therapy was undertaken, with considerable misgivings because of the questionable response of this type of tumor[1] and because of the known effect of x-radiation on the crystalline lens. The patient was observed at three-month intervals, and x-ray therapy was given in conjunction with each visit. These treatments were discontinued in 1943.

On May 18, 1933, the visual acuity was a poor 6/30. There was essentially no change in the size of the tumor. A small hemorrhage had developed on the anterior surface of the tumor. This hemorrhage persisted until October, 1934. At this time a few more capillaries had appeared on the surface of the mass, and they seemed to be compressed by the posterior surface of the cornea. On Dec. 14, 1934, the vision had dropped to 6/45. The upper border of the mass at this time had a grayish color, and the tumor then gave the impression of extending forward from the ciliary body. The intraocular tension was 20 mm. (Schiøtz). On Jan. 23, 1935, the visual acuity was 6/60+. At this time the vascular loops previously noted on the surface had decreased in number. By Dec. 30, 1935, the mass had extended 2 mm. beyond the pupillary border and on the

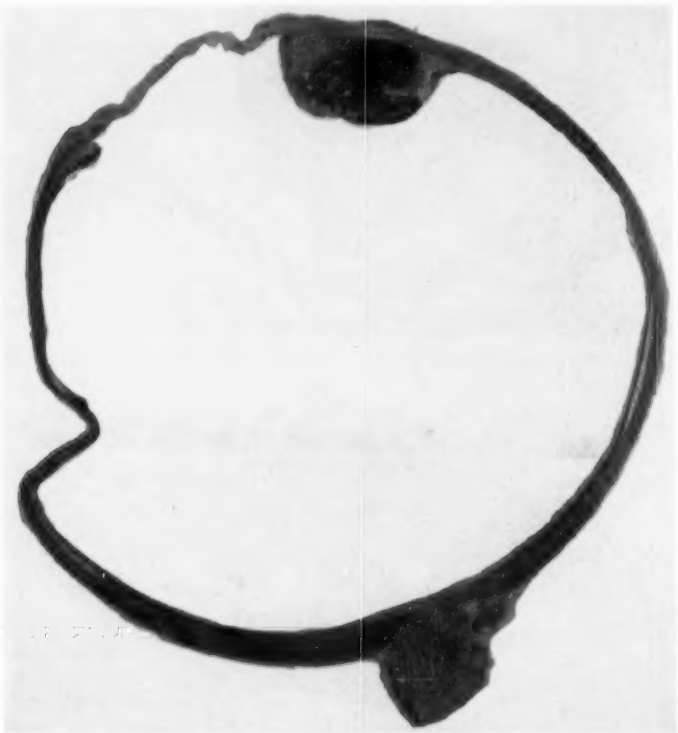


Fig. 3.—Pathologic cross section of eye with tumor. Reproduced from Kodachrome.

whole appeared larger in volume. On June 7, 1936, the lens showed increased cloudiness. There was an amber-colored nucleus, most pronounced adjacent to the tumor site, and the visual acuity had dropped to 5/60. From Nov. 11, 1939, to March 30, 1940, the patient had lost 20 lb. (9.1 kg.) in weight, and it was thought the basis of this symptom was a severe pneumonia she had suffered a month before. Her medical examination revealed no evidence of metastasis. By this time the cornea overlying the tumor had become more opaque, together with increased degeneration in the cornea. The visual acuity was then reduced to light perception only.

On Aug. 15, 1944, after much deliberation and consultation with the family, and with the patient's full knowledge of the risks involved, a cataract extraction was suggested. The patient had regained some of her weight loss and was in fair physical condition except for the hypertension. Inasmuch as the pupil would not dilate well in the area of the tumor, and the tumor was too large to remove, it was elected to do a complete iridectomy in the upper outer quadrant

opposite the site of the tumor, rather than at the classical 12 o'clock position. A keratome incision was made in this quadrant and enlarged laterally with scissors. The iridectomy was performed, and the posterior synechia was freed without hemorrhage. The lens was delivered intracapsularly by the tumbling technique, with little difficulty. The preplaced corneal-scleral sutures were then tied and a bandage applied. Not only did the surgery proceed without complications, but the entire postoperative period was most tranquil. The eye exhibited minimal reaction, and the tumor did not seem to be in the least affected by the added insult of manipulation. The patient was hospitalized for 10 days, and the sutures were removed in two weeks. A preliminary visual check gave vision of 6/12 at this time. An adhesion subsequently developed between the anterior surface of the vitreous and the iris at the site of the original posterior synechia. The vitreous seemed to be pulled forward at this point, but no evidence of uveitis could be observed. In September, 1944, a +11.25 D. sphere was prescribed, which brought her visual acuity to 6/6. The absence of any astigmatism at this time was surprising.

The patient was again carefully observed at three-month intervals. On Nov. 13, 1949, more vascularization was noted at the pupillary border of the tumor. The cornea overlying the mass

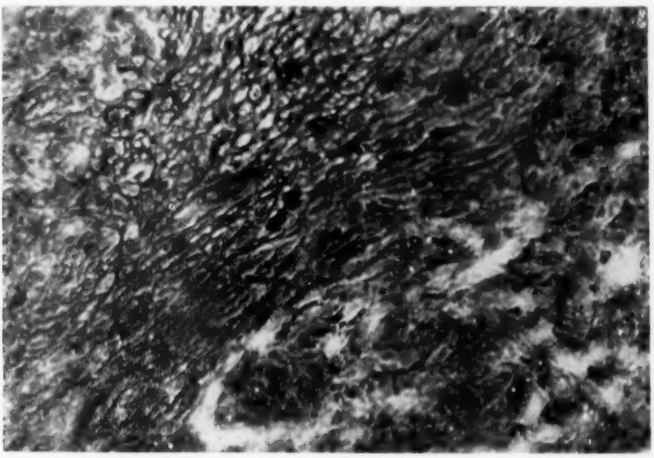


Fig. 4.—Photomicrograph of tumor section. Wilder stain.

had become more opaque and the vitreous-iris adhesion denser. Her lens was changed on March 1, 1948 to +11.25 sph. ⌒ 1.75 cyl., ax. 15, the correction again bringing the vision to 6/6. A cylinder was accepted for the first time since the cataract extraction.

The last examination was made on Nov. 3, 1951. The tumor then measured 8 mm. in length, extending in the sphere-like mass 2 mm. beyond the pupillary border. The chamber angle adjacent to the tumor was completely filled with tissue, but gonioscopic examination did not show extension beyond the immediate area.

After the operation the patient frequently complained of an "aching" type of pain in the eye, although the tension never went above 22 mm. Hg (Schiøtz). In the years of her reduced vision, prior to surgery, the patient had learned to read in Braille, and she preferred to do this despite persistent 6/6 vision. Her health continued to be good except for a cardiovascular condition accompanied by hypertension. Her physician never had any reason to suspect metastasis. Her weight remained at a constant level except for the 20 lb. weight loss associated with the pneumonia in the winter of 1939, part of which loss she regained during the next few years.

The patient died as a result of a coronary occlusion Feb. 15, 1952, at the age of 77. The eye was removed (by me) at autopsy. There was no evidence of metastatic growth.

Pathology.—The globe was sent to the Institute of Ophthalmology at the Presbyterian Hospital. The report by Dr. Joseph A. C. Wadsworth, and corroborated by Dr. A. B. Reese, is as follows: "There is a well-circumscribed pigmented tumor mass in the region of the iris and ciliary body."

Microscopic Study.—"The cornea appears normal except in the periphery at the point adjacent to the existing tumor, which has extended from the ciliary body into the angle. In this area of the cornea there is some increased cellularity of the corneal stroma and reduplication of Descemet's membrane. Descemet's membrane extends normally along the posterior surface of the cornea but splits and covers the outer surface of the tumor. Arising in the anterior portion of the ciliary body is a deeply pigmented tumor, consisting mostly of large chromatophores with well-formed branching processes. The anterior portion of the tumor is less pigmented. The cells are arranged in nests, and there is very little supportive tissue. The cells are large and epithelioid in character. They show evidence of invading the trabeculae and the iris. Schlemm's canal is filled with these tumor cells. On the cornea opposite the tumor there is a well-healed scar, which is probably the cataract incision. Basilar iridectomy had been performed in this area. In the posterior portion

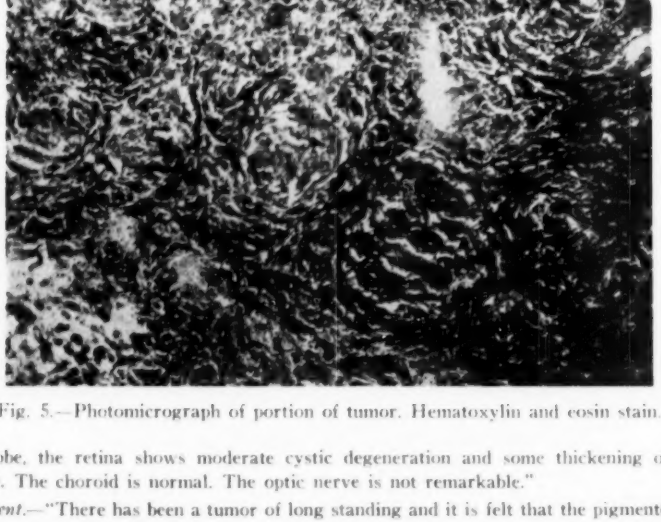


Fig. 5.—Photomicrograph of portion of tumor. Hematoxylin and eosin stain.

of the globe, the retina shows moderate cystic degeneration and some thickening of Bruch's membrane. The choroid is normal. The optic nerve is not remarkable."

Comment.—"There has been a tumor of long standing and it is felt that the pigmented portion of the tumor most probably indicated that part which has increased in size. The cataract extraction has been performed without complications."

Diagnosis.—"Malignant melanoma of the ciliary body and of the iris."

GENERAL COMMENT

Had this patient presented herself at the original examination with two eyes, there would have been no question as to the recommended course of action. However, she was quite firm in her decision to retain the remaining eye despite any possible threat to her general well-being. One might well have refused to become embroiled in such a predicament, but also one might argue that in consideration of the patient's firm conviction, and because she had already suffered the loss of one eye, some policy of procrastination or temporary delay in enucleation could be within the realm of reason.

After consultation with several colleagues, a course of x-ray therapy was decided upon. We realize that if the tumor was a melanoma this procedure would be of little value, since melanoma cells are known to be extremely resistant to x-radiation. Unfortunately, the treatment folder was destroyed in the reorganization of the x-ray department, and the dosage schedule is therefore not available. However, I doubt whether it really had any great effect on the course of the tumor. The dose was considered "mild" by the therapist. At no time was there any local reaction. We realized that the x-ray therapy might well hasten the development of a cataract, which in all probability it did. As it turned out, however, with the fortunate result on the cataract extraction, the earlier surgery gave this patient several more years of useful vision.

The actual duration of the tumor is a matter of interesting speculation. The growth was under my personal observation from May, 1932, until the patient's death, in February, 1952, a little less than 20 years. Since the tumor was of considerable size on her initial visit, we can certainly credit the personal communication of another ophthalmologist, who had seen it seven or eight years previously. During the period under my observation, the tumor showed very little tendency to increase in size. In short, it must have been present for a number of years prior to the 27 or 28 years of reliable observation. If one can credit at all the husband's story of noting a pigmented area on the iris in the exact location of the tumor prior to their marriage, the cycle can be extended another 25 years. This latter deduction is, of course, only conjecture. Interestingly enough, Mayou [3] reports a case of a nevus of the iris which became a melanoma during a 13-year period under his personal observation. Coates [4] also reports 7 out of 26 cases of apparently innocent nevi becoming malignant.

Melanomas of the choroid, ciliary body, and iris have been notoriously unpredictable in respect of metastasis. It is generally believed that melanoma of the choroid disseminates earlier than do similar tumors located farther forward in the uveal tract. Chisholm [5] has recently published a long-term follow-up on the Terry-Jones series, first reported in 1935. The potential degree of malignancy of the various Callender types was substantiated, although two cases of metastasis of spindle Type A were reported. This case represents a spindle type of tumor, although epithelioid cells were prevalent. Death occurred in an average of four years in similar cases of this type. Several cases of late metastatic growth following enucleation for malignant melanoma have been reported. Chisholm (Case 39) reports metastasis 36 years following enucleation in a known fascicular type and quotes Pawel (1900), who reported metastasis 24 years later. Hall [6] (1950) records a case of death from disseminated melanoma 30 years after the original enucleation. This latter case has several loopholes, in that the melanoma was discovered in the stump of the optic nerve at autopsy and was not diagnosed in the eye at the time of enucleation. In a case followed at Wills Eye Hospital (1942) the tumor took 10 years to extend along the optic nerve to the brain. In spite of these case reports of long-standing melanomas, many similar iris melanomas are presented in the literature whose rapidity of metastasis is much greater. Nathanson and Welch,[8] in 1937, studied 128 cases and found a five-year death rate of 67.5% and a six-year death rate of 75%.

None of these cases exactly parallel this presentation, as the tumor remained in situ during the entire period of observation and never did metastasize in a manner

that could be recognized at postmortem examination. This malignant melanoma probably arose from a nevus of the iris, which was present from childhood and extended into the ciliary body, causing complete blocking of the chamber angle in its position.

The manner in which this eye withstood surgery is one of the most interesting aspects of the case. No such experience has been recorded, to my knowledge. Many of these tumors metastasize when the thin blood channels rupture and the cells then enter the blood stream and are disseminated. The delivery of the lens was, fortunately, relatively atraumatic, and no hemorrhage or other complications were encountered at surgery.

The tension in this case always remained within normal limits. This is not the usual course when a melanoma involves the iris, for the tumor cells frequently extend to the angle and block the exit of fluid. In this case, too, there was a blocking of the canal of Schlemm and the angle with tumor cells, but only in the area adjacent to the tumor, and this was borne out by the pathological studies.

Pregnancy played no part in the course of the tumor. The patient was 57 years of age when I first saw her, and she had never been pregnant. The fact that these tumors are notoriously sensitive to hormonal changes during puberty and pregnancy makes this point worth mentioning.[9]

Malignant melanoma of the iris is not as rare as thought if one considers the distribution of the uveal tissue in the whole uveal tract. This tumor is relatively more frequent where the uveal tissue is the thickest, and statistics show that 75% of all uveal tumors are in the posterior choroid.[10] The bulk of the uveal tissue is contained in the choroid, and as it extends forward to form the ciliary body and iris the actual amount of uveal tissue decreases. This may be the reason malignant melanomas of the iris are less frequent than tumors of the posterior segment.

CONCLUSIONS

A case is presented to illustrate the unpredictable behavior of malignant melanoma of the iris.

The fact that such a tumor did not metastasize in one case should not be interpreted as advocating conservatism in the handling of malignant melanoma. Enucleation is still advisable.

The cataract extraction suggests that this tumor was not too vulnerable to trauma.

There is a suggestion, too, that the pathological classification and prognosis continue to present a problem for future investigation.

REFERENCES

1. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951.
2. Spaeth, E. B.: A. M. A. Arch. Ophth. **46**:421, 1951.
3. Mayou, M. S.: Brit. J. Ophth. **14**:152, 1930.
4. Coates, G.: Tr. Ophth. Soc. U. Kingdom **32**:165, 1912.
5. Chisholm, J. F.: Am. J. Ophth. **36**:61, 1953.
6. Hall, W. E. B.: Arch. Ophth. **44**:38, 1950.
7. Lehrfeld, L.: Am. J. Ophth. **25**:199, 1942.
8. Nathanson, I. T., and Welch, C. E.: Am. J. Cancer **31**:598, 1937.
9. Pack, G. T., and Scharnagel, I. M.: Cancer **4**:324, 1951.
10. Agatson, S. A., and Gartner, S.: Am. J. Ophth. **22**:1273, 1939.

BENOXINATE (DORSACAINE) FOR RAPID CORNEAL ANESTHESIA

HENRY E. SCHLEGEL Jr., M.D.
AND
KENNETH C. SWAN, M.D.
PORTLAND, ORE.

THIS STUDY of the ocular pharmacology of a new drug, benoxinate (Dorsacaine), is part of a long-range program which has been directed toward finding improved methods and agents for inducing anesthesia local to the eye and its adnexa. Earlier in the program it was demonstrated that various anesthetics differ markedly in their rates of penetration of the cornea.[1] The topical effectiveness of anesthetics was found to be dependent upon good penetrability of the epithelium, as well as upon anesthetic potency. Also, it was demonstrated that differences in the physical properties of drugs largely determine their relative corneal penetrability from a given vehicle. These physical properties, notably lipid solubility and surface activity, depend upon the molecular structure of the compound and are predictable to a certain extent. Anesthetic activity also is attributable to certain molecular configurations.[2]

These facts have simplified the search for new anesthetic drugs. A number of topically effective compounds have been found, but only a few have clinical usefulness. Whereas a certain degree of anesthetic potency and ability to penetrate the corneal epithelium are prerequisites for topical effectiveness, additional factors help to determine the value of a given drug in ophthalmologic practice. For example, the concentrations of the drug which induce effective anesthesia must be tolerable to the tissues. Unfortunately, many effective anesthetics are tissue irritants. One butylisoquinoline derivative penetrated the corneal epithelium readily and induced an intense anesthesia, but the drug was so highly surface-active that even in minute concentration it produced conjunctival irritation and punctate lesions in the epithelium of the cornea.[3]

Reasonable chemical stability in aqueous solution is still another prerequisite for usefulness of a given topical anesthetic. It is almost imperative that these solutions be able to tolerate boiling to permit their sterilization for operative procedures. Also, it is desirable that the compounds have some antibacterial action to help maintain their sterility and to avoid the need for preservatives.

Given, then, a compound which is chemically stable, tolerated by the tissues, and effective topically, still other factors determine the particular clinical use for the drug. In the literature the comparative effectiveness of local anesthetics often is

From the Department of Ophthalmology, the University of Oregon Medical School.

Read before the Section on Ophthalmology at the 102nd Annual Meeting of the American Medical Association, New York, June 4, 1953.

Dorsacaine for these studies was made available through the Smith-Dorsey Company, a division of The Wander Company, Lincoln, Neb.

expressed mathematically. For example, the onset and the duration of action of a given drug often are presented in minutes. Such exact figures have little meaning when applied to topical anesthetics because dosage factors profoundly affect the onset, intensity, and duration of action of a given drug in the cornea. In general, increasing the concentration of the anesthetic in solution and the duration of its contact with the cornea not only will increase the intensity of its peak effect, but also will accelerate the onset of anesthesia and prolong its duration. It is possible, therefore, to compare the relative effectiveness on the cornea of anesthetic drugs only in a general way. Even the meaning of "anesthesia" must be qualified, because the various types of sensory nerve endings are not affected equally. Tactile sensation is lost before pain and the deeper sensations; therefore, anesthesia adequate for tonometry might not permit traction of the conjunctiva with forceps. Finally, many of the local anesthetic drugs have pharmacologic effects other than on the sensory endings. They may induce changes in the pupil or blood vessels, which may limit or enhance their usefulness under certain circumstances.

When the diversity of factors which determine the clinical usefulness and application of topical anesthetics are considered (Table 1), it seems unlikely that there

TABLE 1.—*Factors Determining Topical Usefulness of Local Anesthetics*

1. Epithelial penetration
2. Anesthetic potency
3. Duration of effects
4. Secondary effects, e. g., mydriasis
5. Systemic toxicity
6. Tissue irritation
7. Allergenicity
8. Sterility of solutions
9. Chemical stability in water

can be a single local anesthetic superior to others for all phases of ophthalmologic practice. For these reasons, our researches have been directed toward finding the best agents and the optimal dosage schedules for specific clinical purposes rather than seeking an all-purpose drug. A great need in the daily office practice of ophthalmology is a stable, nonirritating, short-acting drug which rapidly would induce corneal anesthesia without other effects. For this purpose, 0.5% tetracaine hydrochloride in aqueous solution is most commonly used by American ophthalmologists. It is effective, but its solutions are irritating and frequently induce epithelial changes, which are probably due to the high degree of surface activity of the compound. Perhaps the greatest disadvantage of tetracaine has been the development in an increasing percentage of the population of hypersensitivity reactions. A new compound, benoxinate, seems to have advantages over tetracaine for tonometry, gonioscopy, removal of corneal foreign bodies, and short operative procedures on the cornea and conjunctiva, such as the removal of sutures.

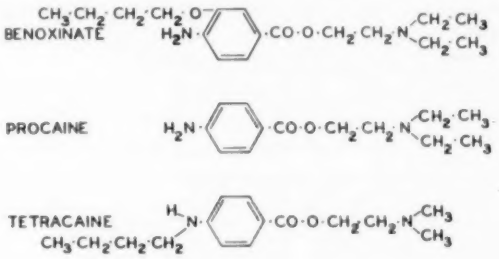
Benoxinate, like procaine, is a benzoic acid ester (Figure). Chemically, it is diethylaminoethanyl *p*-amino-n-butoxybenzoate. The compound was developed in Switzerland, where the hydrochloride salt was known as Novesine. Its ocular effects were described first by Witmer.* Using the Regnier technique on the rabbit cornea, he found the threshold concentration of benoxinate to be 0.2%, as compared with

* Witmer, P.: Personal communication to Dr. George Underwood.

2% for cocaine chloride. His studies on the mouse, rat, guinea pig, and rabbit, utilizing subcutaneous and intravenous injection, revealed the systemic toxicity of benoxinate to be comparable to that of tetracaine.

Witmer noted that 2 drops of 0.5% aqueous solution of benoxinate was well tolerated and induced topical anesthesia of the conjunctiva and cornea of the human eye lasting 20 to 30 minutes. For clinical use, he recommended a 0.1 to 0.2% solution to be used for tonometry and contact-glass examinations. For removal of corneal foreign bodies and for minor operative procedures, such as for pterygium, he advocated the use of as many as 6 to 8 drops to obtain adequate anesthesia.†

Benoxinate has been studied at the University of Oregon Medical School since March, 1952. Its hydrochloride salt is a white powder that is readily soluble in water to form clear, stable solutions, which can be sterilized by boiling. Solutions containing 0.4% benoxinate hydrochloride can be made physiologically isotonic by addition of sodium chloride. They have a pH of 5.4 to 5.5. Surface tension measured with a DuNouy tensiometer is 54 dynes per centimeter at 26 C., as compared with 49 dynes for tetracaine and 72 dynes for procaine. This degree of surface activity would not



be expected to induce irritation and epithelial changes, such as occur with comparable concentrations of tetracaine, but would facilitate wetting of the corneal and conjunctival surfaces by the drug solution. Solutions of 0.4% benoxinate prepared in sterile water do not seem to become contaminated by bacteria, even when left in unstoppered bottles in the laboratory and clinic for weeks at a time. Concentrations of benoxinate above 0.2% inhibited the growth in broth of strains of Micrococcus aureus isolated from patients with blepharoconjunctivitis, whereas 0.2% concentrations did not inhibit all strains. Growth of Pseudomonas aeruginosa in broth was not inhibited completely by benoxinate in 0.4% concentration; however, James found that 0.4% aqueous solutions inoculated with 10,000,000 organisms became sterile in 24 hours, whereas the organisms multiplied in distilled water controls.‡ These studies indicate that benoxinate has significant antibacterial action.

Studies of the penetration of benoxinate into the cornea of the living rabbit eye were made by tissue analysis and compared with the penetration of the standard drug, procaine. Both compounds can be coupled with dye intermediates to form azo dyes suitable for colorimetric determinations. We applied the Bratton and Marshall

† Witmer, P.: Personal communication to Dr. George Underwood.

‡ James, L. H.: Personal communication.

technique for the determination of sulfanilamide to those local anesthetics.§ Minute amounts of these drugs can be detected in the tissues.

The corneas were bathed for three minutes with aqueous solutions containing 1% concentration of the drug, then washed with isotonic saline, and excised for tissue analysis. Concentrations of benoxinate in the intact cornea were found to be about three times as great as that of procaine (Table 2). Concentration of the drugs in the stroma, as compared with that of the epithelium, also was determined (Table 3). The average concentration of benoxinate in the epithelium was almost 10 times as great as in the stroma. These data suggest that benoxinate tends to concentrate in the epithelium and to diffuse from the epithelium into the stroma less readily than procaine.

In another series of experiments the concentrations of benoxinate in the intact cornea were determined at various intervals after a three-minute corneal bath (Table 4). It was found to diffuse out of the stroma very rapidly; therefore, prolonged anesthesia from the topical application of benoxinate would not be expected.

Since the spring of 1952, benoxinate in concentrations of 0.1 to 0.5% has been administered to more than 1,000 individual patients in the eye clinic of the University of Oregon Medical School. A single instillation into the conjunctival sac of a 0.1% concentration from a standard eye dropper generally induces a light surface anesthesia which permits tonometry within a matter of 60 to 90 seconds. The duration of the anesthesia is not more than 10 to 15 minutes. A single instillation of a 0.2% solution induces a more consistent anesthesia, but repeated instillations usually are required before minor surgery, such as removal of a suture or an imbedded corneal foreign body, can be undertaken. A 0.4% solution of benoxinate seems the most suitable concentration for routine office use. This concentration of benoxinate

§ Bratton and Marshall [4]:

METHOD OF TISSUE ANALYSIS

Materials.

Acid-washed carborundum powder
Motor-driven Potter homogenizer
Fisher photoelectric colorimeter

Reagents:

1. 0.1% sodium nitrite
2. 0.1% N(1-naphthyl)-ethylenediamine dihydrochloride
3. 0.5% ammonium sulfamate
4. 15% trichloroacetic acid
5. 95% ethyl alcohol

Tissue Extraction.—The tissue is excised, weighed, and ground in a test tube containing 0.5 cc. of 15% trichloroacetic acid and a small amount of grinding powder. The grinder is then washed with approximately 2 cc. of water and the suspension centrifuged for 12 minutes at 3,000 rpm. The supernatant fluid is decanted and made up to 3 cc. This sample is analyzed in the same manner as a standard aliquot. Filtering may be necessary. Distilled water is used as a blank.

Chemical Analysis.—Three-cubic-centimeter aliquots of standard solutions, containing 1.2% trichloroacetic acid are treated as follows: First, 0.3 cc. of 0.1% sodium nitrate is added for three minutes; then 0.3 cc. of 0.5% ammonium sulfamate is added for two minutes; then, 1.2 cc. of 95% ethyl alcohol, followed by 0.3 cc. of 0.1% *N*(1-naphthyl)-ethylenediamine dihydrochloride is added. Color density, which becomes maximum in 12 minutes and is stable for at least 1 hour, is determined in a photoelectric colorimeter.

is comparable to 0.5% tetracaine hydrochloride in the onset, intensity, and duration of its anesthetic effects, but benoxinate has several advantages. Aqueous solution made isotonic with isotonic saline by addition of sodium chloride produces little or no irritation in uninflamed eyes. Disturbances in the corneal epithelium or hyperemia of the conjunctiva seldom is noted by slit-lamp biomicroscopy after even two or three instillations, whereas these changes seem quite consistent after instillation of 0.5% tetracaine hydrochloride.

TABLE 2.—*Penetration of 1% Aqueous Solutions of Benoxinate and Procaine into Intact Rabbit Cornea After Three-Minute Corneal Bath* *

	Concentration, Mg. per 100 Cc.	
	Range	Average
Benoxinate	17.14-27.06	21.95
Procaine	4.05-13.50	7.39

* Twenty-two determinations.

TABLE 3.—*Distribution of Procaine and Benoxinate in Epithelium and Stroma After Bathing Intact Rabbit Cornea with 1% Aqueous Solutions for Three Minutes* *

	Concentration, Mg. per 100 Cc.			
	Epithelium		Stroma	
	Range	Average	Range	Average
Benoxinate	54.4-93.0	70.6	4.53-10.84	7.55
Procaine	20.0-55.1	38.0	1.92-10.0	5.43

* Thirteen determinations.

TABLE 4.—*Concentration of Benoxinate at Intervals After Bathing Intact Rabbit Cornea with 1% Aqueous Solution for Three Minutes* *

Interval, Min.	Concentration, in Mg. per 100 Cc. (Average)
After 1	21.95
After 15	7.39
After 30	4.24

* Thirty-one determinations.

Concentrations of benoxinate stronger than 0.4% are tolerated in the conjunctival sac but seem unnecessary for routine practice. For tonometry a single instillation of 0.4% benoxinate generally is adequate. If the drop is not well instilled or is squeezed out by blepharospasm, a second drop invariably permits the measurement of the ocular tension and the insertion of a contact lens without delay. When an imbedded foreign body is to be removed from the cornea or a chalazion is to be opened through the conjunctival surface, three instillations at 90-second intervals usually insure adequate surface anesthesia within four to five minutes.

A disadvantage for office use of topical anesthetics such as cocaine and phenacaine has been a slow onset and prolonged duration of their effects, so that an exposure keratitis is prone to develop from diminished winking and drying of the cornea.

In contrast, the anesthetic effects of a single instillation of 0.4% benoxinate largely disappear in 15 minutes. In the concentrations and doses of benoxinate which would be used in office practice no effects upon the blood vessels of the eye, the pupil, the accommodative mechanism, or ocular tension occur.

During the past year over 100 patients with chronic glaucoma received multiple (10 to 100) instillations of benoxinate over a period of 12 months without development of hypersensitivity reactions. Six of this group of patients had developed hypersensitivity to other local anesthetics of the procaine series, most commonly to tetracaine and butacaine. Another patient, a physician, was hypersensitive to this group of drugs and also to cocaine and phenacaine. On three occasions he tolerated instillations of benoxinate without developing a contact dermatitis. This series of patients is too small and the period of observation is too short to permit the conclusion that benoxinate will not induce hypersensitivity reactions, but it does indicate that probably these reactions are infrequent and that cross hypersensitivity does not occur with procaine, tetracaine, and butacaine.

The maximal dose of benoxinate administered at any one time to patients has been 1 cc. of the 0.4% solution, instilled into the lacrimal sac. Excellent anesthesia was obtained for probing and irrigation, without the occurrence of detectable changes

TABLE 5.—*Distribution of Benoxinate and Procaine in Cornea, Iris, and Aqueous of Rabbit Ten Minutes After Subconjunctival Injection of 0.5% Solutions**

	Cornea, Mg./100 Cc.		Iris, Mg./100 Cc.		Aqueous Mg./100 Cc.	
	Range	Average	Range	Average	Range	Average
Benoxinate	12.4-30.5	19.2	3.7-9.4	6.2	0.83-2.2	1.6
Procaine	11.1-29.4	18.1	1.7-8.3	4.1	1.1 -2.1	1.6

* Thirty-one determinations.

in blood pressure, pulse rate, respiratory rate, or temperature. None of these patients noted symptoms suggestive of systemic effects.

In the present studies we have been concerned with those properties of benoxinate which would determine its usefulness in the everyday office practice of ophthalmology; however, it also would seem to be a superior drug for short operative procedures requiring only anesthesia of the conjunctival and corneal surfaces. Administered topically in 0.4% concentration, it would not be suitable for prolonged procedures, such as retinal reattachment operations. For cataract surgery, cocaine generally would be more suitable because it has prolonged effects and also induces vasoconstriction and mydriasis.

The distribution of procaine and benoxinate in the anterior segment of the rabbit eye was determined after injections of 0.3 cc. of 0.5% concentrations under the conjunctival epithelium near the limbus. Tissue analyses were made after 10 minutes. Benoxinate was found to be well tolerated. The two drugs were found to penetrate the globe equally well. Both drugs were found to be present in much higher concentrations in the iris and cornea than in the aqueous (Table 5). This is significant because it casts serious doubt on the value of the time-honored method of evaluating the penetration of drugs into the eye merely by aqueous assays. Further laboratory studies are planned in connection with the distribution of anesthetic drugs in the anterior segment. Also, clinical investigation of benoxinate by injection under the conjunctiva seems justified.

SUMMARY

Good penetrability of the epithelium, as well as anesthetic potency, is a prerequisite to topical effectiveness on the cornea and conjunctiva of a local anesthetic drug; however, to be clinically useful, such a drug must have other favorable properties. It must be nontoxic and well tolerated in concentrations which induce effective anesthesia; also, it must form stable aqueous solutions which tolerate boiling for sterilization. Some antibacterial effects are desirable so that sterility is maintained reasonably well. A drug is most useful in everyday ophthalmologic practice if it rapidly induces surface anesthesia of short duration unaccompanied by other pharmacologic effects on the eye, such as pupillary changes.

Benoxinate (Dorsacaine), a new benzoic acid ester developed in Switzerland, was found to meet the above criteria. Clinical studies indicate that 0.4% aqueous solutions are comparable in anesthetic activity to 0.5% aqueous solutions of tetracaine, but they are less surface-active and, therefore, less irritating and less apt to induce epithelial changes. The hydrochloride salt forms stable aqueous solutions which tolerate boiling and have some antibacterial effects.

Tissue analyses reveal that, in comparison with procaine, benoxinate applied topically rapidly concentrates in the corneal epithelium. This probably accounts for the much greater topical effectiveness of benoxinate. No differences in the distribution of benoxinate and procaine in the anterior segment were found after injection under the conjunctival epithelium, but much higher concentrations of both drugs were present in the iris and cornea than in the aqueous. This suggests that aqueous assays alone are not reliable indices of the penetration of drugs into the intraocular tissues.

ABSTRACT OF DISCUSSION

DR. HAROLD G. SCHEIE, Philadelphia: The authors have evaluated benoxinate, a new local anesthetic agent for surface use in ophthalmology, very logically and critically. They have indicated that in some ways benoxinate is superior to other anesthetic agents which are available. The authors sent a copy of their paper and a supply of the anesthetic agent to me, and I have used the drug on a limited number of patients, as have other members of our staff.

The antibacterial qualities are probably not of too great importance, because other substances can be put into solution in benzalkonium (Zephiran). Benzalkonium causes only slight discomfort upon instillation into the eye and for that reason does save some time in a busy office, for the patient is able to open his eyes for recording of tension more quickly than he can with anesthetics such as tetracaine.

The excellent and rapid penetrating qualities are indicated by the fact that after instillations of benoxinate in one eye and tetracaine in the other one can pick up the conjunctiva with less discomfort in the eye which has received benoxinate.

Benoxinate would seem to be a satisfactory substitute for tetracaine when an allergy to the latter develops. In our experience, however, allergy to tetracaine is very infrequent. I cannot recall more than four or five patients in my rather extensive experience with it.

Of greater importance is the shorter duration of benoxinate. This safeguards the patient, at least somewhat, against injury to his eye with a handkerchief or by incurring a foreign body upon leaving the ophthalmologist's office. This property marks a rather new advent in the field of anesthesiology, because attempts in the past have been directed toward obtaining anesthetic agents of longer duration.

(Slide) The duration can be increased in several ways, one of which is by adding to the carbon chain of procaine. However, the toxicity of the drug is likewise considerably increased, and in many cases this precludes its injection.

More recently, Efocaine has been made available. This consists of a critical solution of procaine, the crystals precipitating out in the tissues once it comes in contact with body fluids. A depot of procaine is therefore formed which maintains (at least theoretically) the anesthetic action of the drug over a period of days.

Recently we have been working with orthoxin, a substance not yet available, which is a diamine without the ester linkage of the procaine group. It has an anesthetic effect two or three times as long as procaine and does not diffuse through tissues quite as well as procaine. I question whether it was valid for the present authors to attempt to compare the diffusion of benoxinate instilled into the eye with that of procaine, because procaine goes through the intact cornea very poorly, although it penetrates tissues fairly well. I think the comparison might better have been made with butacaine or one of the other drugs which we believe provides deep corneal anesthesia.

Dr. Schlegel and Dr. Swan are blazing a pioneer trail in their search for a shorter-acting local anesthetic agent.

Knowing Dr. Swan's ability, I am a little concerned that he might develop an anesthetic agent of such short action that we shall have to use the tonometer with great rapidity to match the short action of the anesthetic.

DR. KENNETH C. SWAN, Portland, Ore.: Thank you, Dr. Scheie, for your pertinent discussion.

Procaine was selected for comparative studies because it has been the standard drug used for penetration studies in other tissues. Procaine does penetrate the cornea but does not concentrate in the epithelium. This seems to be a crucial factor in determining the potency of anesthetics when topically applied.

Dr. Scheie mentioned that few patients in the Philadelphia area develop hypersensitivity to tetracaine; in the Pacific Northwest, however, there is a relatively high incidence of hypersensitivity to this drug. The majority of patients who develop it have had the drug prescribed for home use, usually to permit the wearing of contact lenses or for chronic conjunctivitis. The prescription of local anesthetics is seldom indicated. As Dr. Scheie and Dr. Schlegel have pointed out, there is danger of exposure keratitis as well as the development of hypersensitivity.

There are many potent topical anesthetics, but only a few, like benoxinate, have the physical properties so that they may concentrate in the epithelium and, at the same time, produce little tissue irritation. It would be a tragedy if the usefulness of these few drugs should become limited by their indiscriminate prescription.

REFERENCES

1. Swan, K. C., and White, N. G.: Corneal Permeability: Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043 (Sept.) 1942.

2. Adriani, J.: The Pharmacology of Anesthetic Drugs, Springfield, Ill., Charles C Thomas, Publisher, 1952.

3. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537 (May) 1939.

4. Swan, K. C.: Reactivity of the Ocular Tissues to Wetting Agents, Am. J. Ophth. **27**:1118 (Oct.) 1944.

OUTFLOW OF AQUEOUS HUMOR

Biomicroscopic Estimation Compared with Tonographic Measurement

J. STEPANIK, M.D.
VIENNA
AND
LIEUTENANT (jg) R. A. KEMPER (MC), U.S.N.R.

THE PURPOSE of this work was to determine quantitatively the biomicroscopically visible outflow of aqueous humor in normal eyes and to compare this value with the total aqueous outflow. In other words, we attempted to determine to what extent the clear or almost clear aqueous veins participate in the transport of aqueous.

The first attempt to estimate the flow of aqueous humor was carried out by Hovius,* who opened the anterior chambers of dogs' eyes and measured the aqueous flowing out of the wound. The surprisingly high values which this experiment gave (130 cu. mm. per minute) were correctly attributed to the gross disturbance of the physiologic relationship resulting from opening the anterior chamber.† Direct measurement by cannulating the anterior chamber while maintaining normal intraocular pressure gave essentially lower results (Leber and Benson, Priestly Smith, Niesnamoff ‡). Using the same experimental arrangement, while blocking the chamber angle by means of fibrin, Friedenwald and Pierce § found the outflow of aqueous to be as low as 1.0 cu. mm. per minute. Similar results were obtained by Uribe y Troncoso,[4] who estimated the outflow of aqueous at 2.1 to 5.2 cu. mm. per minute by analyzing diluted blood obtained from the limbal veins of rabbit eyes.

In contrast to these direct methods, more recent methods have been developed for estimating the outflow rate of aqueous in animal eyes by ascertaining the rate of entrance of various substances from the blood into the aqueous humor (Kinsey, Grant, Cogan, and associates ‖; Palm [5]; Ross,[9] and others) or the rate of disappearance of substances from the anterior chamber (Kinsey and Bárány,[7] Davson and Matchett,[10] Ross,[9] and others). These methods have the advantage of causing the least disturbance of the physiologic relationships; hence the results obtained (2.75, 4.0, etc., cu. mm. per minute) probably lie closest to the true values. However, they

Aided by United States Public Health Grant B-158.

From the Department of Ophthalmology, University of Cincinnati College of Medicine.
Formerly Research Assistant, Department of Ophthalmology, University of Cincinnati College of Medicine (Dr. Stepanik). Former resident, Department of Ophthalmology, University of Cincinnati (Lieutenant Kemper).

* Hovius[1]; cited by Leber [2] and Friedenwald and Pierce.[3]

† Leber,[2] p. 225.

‡ Leber,[2] p. 226.

§ Friedenwald and Pierce,[3] p. 552.

‖ Kinsey, Grant, Cogan and others.[5] Kinsey and Grant.[6]

apply only for the eyes of the particular experimental animals observed, and, because of the great difference in anatomic structure,[11] these figures may be applied to the human eye only with the utmost caution. For this reason, it has long been desired to find a method which would permit the determination of the minute volume in living human eyes.

In 1932, Friedenwald and Pierce ¶ succeeded in measuring the minute volume of the aqueous outflow in a single eye (of a child). In this eye an abnormally small lens was luxated into the anterior chamber and blocked the pupil only for certain intervals of time. As a result, during these periods the outflow of aqueous from the anterior chamber was maintained, whereas the inflow of aqueous into the anterior chamber through the pupil was interrupted. Thus, the outflow of aqueous could be estimated from two volume measurements of the anterior chamber taken at two different times. The values obtained were between 1.5 and 2.5 cu. mm. per minute.

It was not until 1950 that two methods for estimation of the total outflow of aqueous from human eyes were described: the fluorescein method (Goldmann [12]) and Grant's tonography.[13]

In the first method, fluorescein is injected intravenously. Repeated measurements are made of the concentration of free fluorescein (not combined with albumin) in the ultrafiltrate of the blood. These concentrations are compared with the fluorescein concentration in the aqueous of the anterior chamber by means of suitable calculations which give the aqueous outflow rate. With this method, in 10 normal eyes minute volumes of 1.1 to 2.5 cu. mm. per minute were found, with an average of 1.9 cu. mm.

Tonography was devised originally to estimate the resistance which the aqueous has to overcome when leaving the eye. Owing to the fact that the values for outflow rate are determined for given values of intraocular pressure and resistance, a simple mathematical formula could be devised (Grant [14]) which permits the calculation of the outflow from the results of a single tonographic determination.

After the discovery of the aqueous veins, Ascher, in 1942,# suggested that the minute volume of the aqueous outflow could be estimated from the sums of the minute volumes of all aqueous veins. He based this on approximate calculations showing that a single large aqueous vein could carry more than half the total outflow.

For calculation of the minute volumes of the aqueous veins, he used values which had been found for the blood veins of the human conjunctiva, viz., for the velocity of current the values given by Zeller [16] of 0.7 to 1.3 mm. per second, and for the diameters the values given by Leber * of 0.01 to 0.1 mm. For the total aqueous outflow, Ascher accepted the previously mentioned value of 1.5 cu. mm. per minute. He figures a minute volume of 0.848 cu. mm. per minute for one aqueous vein having the maximum values for diameter and speed of flow, and of 0.0008 cu. mm. per minute for a small aqueous vein with low velocity of flow. Considering the figures published by Dvorak-Theobald, Ascher stated that 20 canal outlets of smallest size could eliminate 0.126 cu. mm. per minute but that a single outlet of widest cross section could eliminate as much as 0.891 cu. mm. per minute. Considering these very different figures, Ascher thought that on the average an

¶ Friedenwald and Pierce,[3] p. 556.

Ascher,[15] p. 1192.

* Leber,[2] p. 63.

approximate accord could be reached between the amount of fluid eliminated by aqueous veins and the estimation by Friedenwald and Pierce.

De Vries,[17] who followed these ideas further (1947), was able to calculate the minute volume for four aqueous veins of different eyes, in which he could measure the speed of flow with the aid of spontaneously entering blood waves,† which he designated as "projectiles." Using the average value of these four measurements and the average number of aqueous veins per eye, he obtained a visible aqueous outflow of 1 to 2 cu. mm. per minute per eye.

By the introduction of artificially produced projectiles for the determination of the current velocity in aqueous veins, one of us (J. S.) [18] has succeeded in carrying out the above-mentioned suggestion of Ascher.‡ Therefore, with the tonography of Grant, all conditions are suitable at this time for assessing the total aqueous outflow and comparing it with the visible outflow through clear or practically clear aqueous veins. It is important to note that the visible aqueous outflow is the sum of (*a*) the outflow in the clear, or practically clear, aqueous veins plus (*b*) the outflow in aqueous veins which contain blood mixed with aqueous. To estimate the latter portion of the outflow, it would be necessary to judge the per cent of aqueous humor streaming in an individual vessel from the color of its content. Such a judgment would be subject to extremely large errors, however, and for this reason we made no attempt to estimate the aqueous outflow through these vessels. Our figures for visible outflow are therefore "minimum" values; the true values for outflow through all aqueous veins are doubtless higher.

PROCEDURE

A. Determination of the Visible Aqueous Outflow (VO).—The visible aqueous outflow of an eye is given by the sum of the minute volumes of its aqueous veins. For this determination, therefore, we first carefully searched each eye for aqueous veins and recorded these in sketches. Next, we determined the current velocity with the aid of artificially produced projectiles, a method which has been described in detail elsewhere.[18] By briefly touching the aqueous vein upstream from its junction with a small blood vessel, a small group of blood cells (a "projectile") can be produced in the aqueous vein, and can be observed moving downstream at a velocity which can be determined. First, by a preliminary touching of the aqueous vein, one must learn with how long a touch and in what place the projectile can be produced; then one must measure the usable section of the aqueous vein downstream from the point of origin of the projectile. A newly produced projectile is followed through this section (l), and the time (t) for the passage of the projectile, is determined by a stop watch. The velocity of the projectile, $v = \frac{l}{t}$, can be taken as the average stream velocity.[18] By this method the stream velocities could be determined in 60 out of 67 veins.§ In five aqueous veins which were shorter than 1 mm., and in two others, in which no projectiles could be produced, the average value for the stream velocity, 4.6 mm. per second, was used for the calculation of the minute volume. Such values are marked with asterisks in Table 1. The average error in the determination of the stream velocity was estimated as 19.2% (ranging from 5 to 50%).

† Ascher,[15] p. 1202.

‡ Ascher,[19] Ascher and Spurgeon.[20]

§ The results of the measurement of these vessels will be published in more detail elsewhere.[18]

TABLE 1.—*Visible and Total Outflow of Aqueous of Normal Eyes**

	Aqueous Veins									
Eye No.	No.	*d*, Mm.	*v*, Mm./Sec.	Min. Vol., Mm.³/Min.	*Q* Aqu. Vein M.V. 100/*To*	*VO* Mm.³/Min.	*TO* Mm.³/Min.	*Q* Eye *VO* 100/*TO*	*C* Mm.³/Min.	*IOP* Mm./Hg
1	1	0.050	4.5	0.53	14.0	1.13	3.70	30.5	0.31	17.4
	2	0.050	5.1	0.60	16.0	....	....	....	....	....
2	3	0.050	2.5	0.29	7.4	0.29	3.90	7.4	0.28	19.3
3	4	0.035	7.6	0.44	21.0	1.08	2.05	52.7	0.15	21.0
	5	0.035	5.3	0.31	15.0	....	....	....	....	....
	6	0.035	5.7	0.33	16.0	....	....	....	....	....
4	7	0.070	5.9	1.36	57.6	1.36	2.36	57.6	0.22	18.8
5	8	0.035	5.7	0.33	13.0	0.87	2.40	36.0	0.23	20.1
	9	0.050	4.6†	0.54	22.0	....	....	....	....	....
6	10	0.035	3.8	0.22	7.6	0.22	2.90	7.6	0.13	28.7
7	11	0.035	5.4	0.31	9.1	0.31	3.40	9.1	0.17	26.9
8	12	0.050	6.8	0.80	33.0	1.52	2.41	63.1	0.18	20.2
	13	0.035	2.8	0.16	6.6	....	....	....	....	....
	14	0.050	2.5	0.29	12.0	....	....	....	....	....
	15	0.035	4.6†	0.27	11.0	....	....	....	....	....
9	16	0.050	7.6	0.90	23.0	1.03	3.90	26.4	0.33	17.2
	17	0.035	2.3	0.13	3.3	....	....	....	....	....
10	18	0.050	7.6	0.90	21.0	0.90	4.20	21.0	0.26	18.2
11	19	0.050	6.6	0.78	21.0	0.78	3.70	21.0	0.18	28.5
12	20	0.050	6.7	0.79	22.0	1.71	3.60	47.5	0.26	20.4
	21	0.050	5.0	0.59	16.0	....	....	....	....	....
	22	0.035	5.7	0.33	9.2	....	....	....	....	....
13	23	0.035	6.4	0.37	10.0	2.43	3.52	69.0	0.34	15.0
	24	0.035	5.7	0.33	9.4	....	....	....	....	....
	25	0.035	3.8	0.22	6.2	....	....	....	....	....
	26	0.070	6.5	1.51	42.9	....	....	....	....	....
14	27	0.035	5.0	0.29	9.7	1.46	3.00	48.6	0.25	18.9
	28	0.035	1.4	0.08	2.6	....	....	....	....	....
	29	0.050	4.6	0.54	18.0	....	....	....	....	....
	30	0.050	4.7	0.55	18.0	....	....	....	....	....
15	31	0.070	4.5	1.04	35.7	1.04	2.91	35.7	0.21	20.1
16	32	0.035	4.6†	0.27	10.0	1.74	2.70	64.4	0.25	16.9
	33	0.070	3.8	0.88	32.0	....	....	....	....	....
	34	0.050	5.0	0.59	21.0	....	....	....	....	....
17	35	0.050	3.8	0.45	16.0	0.52	2.81	18.0	0.25	16.5
	36	0.035	1.3	0.07	2.0	....	....	....	....	....
18	37	0.050	2.5	0.29	10.0	0.29	2.71	10.0	0.16	24.4
19	38	0.070	5.4	1.25	46.5	1.84	2.69	68.4	0.28	14.2
	39	0.050	5.0	0.59	21.0	....	....	....	....	....
20	40	0.035	4.6†	0.27	8.1	1.97	3.32	59.3	0.20	24.4
	41	0.050	5.0	0.59	17.0	....	....	....	....	....
	42	0.035	4.7	0.27	8.1	....	....	....	....	....
	43	0.035	3.8	0.22	6.6	....	....	....	....	....
	44	0.050	5.3	0.62	18.0	....	....	....	....	....
21	45	0.035	2.0	0.12	6.2	0.90	1.94	46.0	0.16	19.0
	46	0.035	4.6†	0.27	14.0	....	....	....	....	....
	47	0.050	4.3	0.51	26.0	....	....	....	....	....
22	48	0.050	6.0	0.71	49.0	0.71	1.44	49.0	0.24	10.0
23	49	0.035	3.0	0.17	7.8	0.37	2.19	16.0	0.13	22.7
	50	0.035	3.4	0.20	9.1	....	....	....	....	....
24	51	0.035	5.0	0.29	17.0	0.29	1.68	17.0	0.10	25.1
25	52	0.035	4.4	0.25	6.1	0.97	4.10	23.0	0.26	23.2
	53	0.050	3.8	0.45	11.0	....	....	....	....	....
	54	0.035	4.6†	0.27	6.0	....	....	....	....	....
26	55	0.035	3.0	0.17	6.5	0.17	2.61	6.5	0.13	24.8
27	56	0.035	5.7	0.33	13.0	1.12	2.45	45.7	0.22	17.6
	57	0.035	4.4	0.25	10.0	....	....	....	....	....
	58	0.050	4.6†	0.54	22.0	....	....	....	....	....
28	59	0.025	3.4	0.10	4.6	1.01	2.18	46.3	0.15	22.3
	60	0.070	3.0	0.69	31.0	....	....	....	....	....
	61	0.035	3.8	0.22	10.0	....	....	....	....	....
29	62	0.050	6.3	0.74	26.0	1.60	2.80	57.0	0.18	20.1
	63	0.035	5.3	0.31	11.0	....	....	....	....	....
	64	0.070	2.0	0.46	16.0	....	....	....	....	....
	65	0.025	3.2	0.09	3.0	....	....	....	....	....
30	66	0.050	5.0	0.59	23.0	0.97	2.51	38.0	0.18	21.0
	67	0.035	6.5	0.38	15.0	....	....	....	....	....

* *d* indicates width of aqueous vein, in millimeters; *v*, velocity of the projectile, in millimeters per second; Min. Vol./Aqu. Vein, visible outflow, in cubic millimeters per aqueous vein per minute; *Q*/Aqu. Vein, visible outflow per aqueous vein, expressed in per cent of the total aqueous outflow; *VO*, visible outflow, in cubic millimeters per eye per minute; *TO*, total aqueous outflow, in cubic millimeters per eye per minute; *Q*/Eye, visible outflow per eye, expressed in per cent of the total aqueous outflow; *C*, coefficient of facility of outflow, in cubic millimeters per minute; *IOP*, intraocular pressure, in millimeters of mercury.

† Average stream velocity.

The diameters of the aqueous veins were measured with an ocular micrometer, approximately in the middle of section 1. The estimated error of ± 0.01 mm. is very high, percentagewise, for measurement of small diameters. It is mainly caused by the movement of the patient's eye. We are trying to substitute a suitable photographic method for this measurement. The average error in the determination of the diameters amounted to 24.2% (ranging from 14.3 to 40%).

The values of l, d, and t are averages of two to three measurements.

The minute volumes were calculated from the values thus obtained for the stream velocity and the diameter of the aqueous veins. For that purpose we used the formula:

$$V \text{ (mm.}^3\text{/min.)} = \pi r^2 v,$$

in which r is the radius of the aqueous vein and v is the velocity of the projectile (average stream velocity). In this formula the elliptical cross section of the aqueous vein and the possible viscosity changes of the aqueous humor due to varying admixture with blood are not considered. The calculated minute volumes could only be identified with the volume of aqueous flowing out through these vessels if their content actually were only aqueous. This is true only for completely clear aqueous veins, which, however, are relatively rare. The visible blood cells in most of the aqueous veins which we investigated indicate a relatively slight blood content, which could not be determined and was neglected in the calculation of the minute volumes.

B. Determination of the Total Aqueous Outflow (TO).—The total aqueous outflow was determined by Grant's tonographic method. For calculation of K we used the formula given by Grant [13]:

$$K = (p_0 - 4)\ C$$

where K is the aqueous outflow in cubic millimeters per minute, p_0 is the tension of the eye at the beginning of the tonography, and C is the coefficient or the facility of outflow and corresponds to the amount of aqueous which flows out per minute and per millimeter Hg pressure increase during the tonography. At this point we shall not discuss how far it is permissible to assume as correct the total outflow determined by the tonographic method and shall refer in this connection to Friedenwald's discussion of Grant's paper.[14]

On each eye we carried out three tonographic determinations and used the average value of K as the total outflow (TO) of this eye. The average error for the tonography, according to Kronfeld,[21] amounts to 10 to 25%. Likewise, the values given in the Tables for C and the tension (IOP) are average values of three measurements.

C. Determination of the Q Ratios.—The visible aaqueous outflow expressed as percentage of the total aqueous outflow gives the value which we have designated as Q.

$$Q = VO \times 100/\ TO.$$

RESULTS

The measurements discussed above were carried out on 67 aqueous veins, clear or almost clear, in 30 normal eyes of 14 female and 8 male patients, whose ages varied from 46 to 82. The results per vein and per eye are shown in Table 1. In Columns 3 and 5 the minute volumes for the visible aqueous outflow per vessel and

per eye are given; in Columns 4 and 7 are the corresponding values for Q. In Columns 6, 8, and 9, the average values of the results of the three tonographic examinations per eye are listed.

The maximum, minimum, and average values of our results are collected in Table 2.

The smallest visible outflow was found in Eye 26: 0.17 cu. mm. per minute, corresponding to a single aqueous vein of 0.035 mm. diameter and 3.0 mm. per second stream velocity. This eye also had the smallest Q value, 6.5. For this eye, the average value for C was 0.13; for the tension, 24.8 mm. Hg.

The largest visible outflow of 2.43 cu. mm. per minute was found for Eye 13; it had four aqueous veins, three with the same diameter, 0.035 mm., but current

TABLE 2.—*Visible and Total Outflow of Aqueous in Normal Eyes: Maximal, Minimal and Average Values*

		Maximum	Minimum	Average
Aqueous veins	Mm.³ Vol., Mm.³ Min.	1.51	0.07	0.45
	$\frac{Q}{\text{(M. V. 100 } TO)}$	57.7	2.6	16.4
Eyes	$\frac{VO}{\text{Mm.}^3\text{ Min.}}$	2.43	0.17	1.02
	$\frac{Q}{(VO.\ 100\ TO}$	69.0	6.5	36.8
	$\frac{TO}{\text{Mm.}^3\text{ Min.}}$	4.2	1.44	2.83

TABLE 3.—*Relation of Visible Outflow of Aqueous to Coefficient of Facility of Outflow and to the Intraocular Pressure*

Number of Eyes	VO Mm.³ Min.	C* Mm.³ Min.	IOP.* Mm. Hg
Group I (14 eyes)	> 1.02	0.24	18.7
Group II (16 eyes)	< 1.02	0.19	22.0

* Average values.

velocities of 3.8, 5.7, and 6.4 mm. per second; the fourth had a diameter of 0.07 mm. and a stream velocity of 6.5 mm. per second. This eye showed the highest Q value, 69.0. The value for C was 0.34; and for the tension, 15.0 mm. Hg.

Eye 19, with two aqueous veins of 0.07 and 0.05 mm. diameter and stream currents of 5.4 and 5.0 mm. per second, showed an almost equally high Q, of 68.4. The visible aqueous outflow amounted to 1.84 cu. mm. per minute; the value for C 69.0. The value for C was 0.34, and for tension, 15.0 mm. Hg.

In general, in eyes with good visible outflow (> 1.02) we found only one C smaller than 0.18, but often C values of 0.25 and more. The tension was, as a rule, lower than the average value, frequently considerably lower.

The relationships between the visible outflow (VO) and the values for C and IOU, mentioned in the preceding paragraphs, are confirmed by Table 3: eyes with a visible outflow greater than the average value, 1.02 (Group 1), have on the average a clearly higher value for C and a lower intraocular pressure than eyes with

a visible outflow smaller than 1.02 (Group II). The fact that a smaller visible outflow is not always coupled with higher tension and a lower C is proved by Eyes 2 and 17 (Table 1).

The Q values give the answer to the principal question of our investigation: To what extent do the clear aqueous veins of an eye, singly or together, participate in the total outflow of the aqueous? These Q values show large variations: From a minimum of 2.5% (Vessel 36) the participation of a single vessel in the transport of aqueous increases to a value of 57.6% (Vessel 7). The effects of diameter and stream velocity on the Q values are independent of each other. A small Q value, for instance, may be caused by a small diameter in the case of an average stream velocity (Vessels 59 and 65), but also by a remarkably low stream velocity in a wider vessel (Vessels 3, 28, and 36). In addition, the stream velocity can be low in one aqueous vein, whereas it is two to three times as fast in other aqueous veins of the same eye; thus the Q of the first vessel can be small and that of the other considerably higher (Eyes 14 and 17). Corresponding to these relationships the number of aqueous veins alone will not be decisive for the Q of an eye. However, if we divide the eyes into groups according to the number of aqueous veins (Table 4), we see that the minimum, as well as the average, Q value is smallest for the group with one aqueous vein and becomes higher with increase in the number of vessels in other groups. The Q values in each of these groups are subject to very large variations and reach maximum values that are approximately equal.

TABLE 4.—*Relation of Visible Outflow of Aqueous to Number of Aqueous Veins per Eye*

No. of Aqueous Veins per Eye	Q Eye: Visible Outflow per Eye, Expressed in Per Cent of Total Aqueous Outflow									Maximum	Average
1	6	7	9	10	17	21	21	35	49	57	22
2	16	18	26	30	36	38	..	..	..	68	33
3	23	45	46	46	47	52	..	..	..	64	46
4	48	57	64	64	..	..	..	..	..	69	60
5	(59)	..	..	..	..	..	..	..	..	(59)	(59)

COMMENT

In considering the high Q values that we found for some clear or almost clear aqueous veins, it is not immediately understandable why such a disproportionately high percentage of the aqueous should flow through those vessels which numerically represent only a fraction of the many pathways for outflow. Ascher (personal communication) considers that these vessels will be preferred for outflow because they present the lowest resistance. This may be supported by the following anatomical considerations.‖

The well-known connections between Schlemm's canal and the episcleral veins consist of two parts: (*a*) the outlets, and (*b*) the deep intrascleral venous plexus and their anastomoses with the episcleral veins.

The outlets are short endothelial tubes originating with a relatively narrow, elliptical lumen from Schlemm's canal, showing a conical form, and emptying into the deep intrascleral venous plexus. Their number is 20 to 30 per eye.

‖ Leber,[2] p. 67. Henderson,[22] cited by Uribe y Troncoso.[4] Maggiore.[23] Dvorak-Theobald.[24]

The intrascleral venous plexus has been described as a network of varicosely widened veins in which the continuity is interrupted by small reticula. The blood leaves this plexus through veins which run obliquely through the sclera and reach the surface of the sclera, as well as the episcleral venous network at a greater distance from the limbus, although still preequatorially. In addition, there have also been found, between the intrascleral and the episcleral venous network, occasional anastomoses which, in places, form small varicosities and finally pass almost directly through the sclera. Often they pierce the sclera, forming a figure six or eight. These were identified biomicroscopically with aqueous veins of limbal origin.¶ Finer anastomoses enter the limbal sections of the episcleral and conjunctival venous network and produce the aqueous veins which come from the limbal meshwork.¶

Corresponding to this anatomical structure there are 20 to 30 parallel-connected pathways in the region of the outlets and still more in the region of the intrascleral venous plexus which, by analogy with Kirchhoff's law, will deliver aqueous in quantities inversely proportional to their resistances. Assumed that the pressure is the same in all episcleral veins, the pressure drop between the beginning and the ending of the pathways will be the same. The resistances in these vessels will differ, being inversely proportional to the fourth power of the radius and directly proportional to the length of these vessels. In the region of the outlets, which are short and cone-shaped, the resistance will be determined mainly by the narrowest part, the outlet opening, the size of which is subject to great variations: Whereas there is a large number of small outlets, the large outlets are seldom found. Thus, the delivery of a high percentage of aqueous by a single large outlet is possible.#

For the aqueous leaving one outlet there are available, in the intrascleral plexus, several parallel-connected pathways through which the aqueous will be partitioned, in inverse proportion to the resistance. If an aqueous vein is present in this region and directly connected with the corresponding outlet, then, equal diameters assumed, it will be preferred on account of its short length, in comparison with the other branches of the intrascleral plexus. Besides, if the aqueous vein is wider than the other branches of the intrascleral plexus in this region, the resistance will be essentially less in this aqueous vein in comparison with the other deeper pathways and a high percentage of the aqueous coming from the outlet will pass through it. An anatomical specimen of such an aqueous vein was shown by Ashton[25] in a Neoprene cast.

In a sector where no anastomoses are present near the limbus, the aqueous will prefer, to other branches, the shortest and widest branch of the intrascleral plexus: an aqueous vein from a scleral emissary.

In all cases, however, by analogy with Kirchhoff's law, a certain percentage of the aqueous will flow out through the other branches of the intrascleral plexus. Other conditions being equal, the portion of aqueous per vessel will be very small, due to the large number of these branches. For this reason, as well as the longer intrascleral passage, the aqueous flowing in these vessels will already be homogeneously mixed with blood before leaving the sclera and can no longer be detected biomicroscopically.

¶ Ascher,[15] p. 1181.

Ascher.[15] Ascher and Spurgeon.[20]

From these considerations, it follows that the "loading" of a single aqueous vein with a high percentage of the total outflow is possible; however, in order for this to occur two favorable factors must be present at the same time, namely, a wide outlet and a connecting wide aqueous vein. Thus, the aqueous veins with limbal origin will probably offer the most favorable conditions for outflow.

All aqueous veins showing a Q of more than 30 (Vessels 7, 12, 26, 31, 33, and 38) originated in the limbus near the horizontal meridian. Five were located nasally at 8:00, 8:00, 8:30, 4:00, and 4:00 o'clock and one temporally at 4:00 o'clock. Since, according to the findings of Dvorak-Theobald,[24] the largest outlets likewise are present near the horizontal meridian, the considerations presented above could explain the high Q of these vessels. Low resistance to aqueous outflow therefore seems to be connected with favorable anatomical outflow conditions.

From the outflow conditions described, it can further be assumed that the visible outflow in clear and almost clear aqueous veins can never reach the values of the total aqueous outflow. This holds true for all of our measurements.

SUMMARY

By the method of artificially produced projectiles (Stepanik[18]) we have estimated the biomicroscopically visible aqueous outflow through the clear or almost clear aqueous veins in 30 normal eyes and compared it with the values of the total aqueous outflow determined by tonography. This visible outflow ranged from 6.51 to 69.02% of the total aqueous outflow and did not in any eye reach or exceed the value of the latter. We assume that another portion of the superficially outflowing aqueous is already mixed with blood and therefore cannot be observed. The dependence of the values for the visible aqueous outflow on the anatomic relationships of the outflow pathways is discussed in detail. The comparison of the values of the visible aqueous outflow with C (coefficient of facility of outflow) has shown that a higher visible aqueous outflow may be connected with a larger C (lower outflow resistance). However, the accuracy of measurement of both quantities must be improved before this can be stated with certainty.

K. W. Ascher, M.D., and W. M. Spurgeon, Ph.D., gave helpful advice.

REFERENCES

1. Hovius: De circulari humorum ocularium motu, Traj. ad Rhenum, G. van de Water, 1702.

2. Leber, T.: Die Zirkulation und Ernährungsverhältnisse des Auges, in Graefe, A., and Saemisch, O.: Handbuch der gesammten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1903.

3. Friedenwald, J. S., and Pierce, H. F.: The Circulation of the Aqueous: I. Rate of Flow, Arch. Ophth. **7**:538-557, 1932.

4. Uribe y Troncoso, M.: Neue Untersuchungen über die Saftströmung im lebenden Auge und in anderen Organen und ihre Messungen, Klin. Monatsbl. Augenh. **53**:1-29, 1914.

5. Kinsey, V. E.; Grant, W. M.; Cogan, D. G.; Livingood, J. J., and Curtis, B. R.: Sodium Chloride and Phosphorus Movement and the Eye, Arch. Ophth. **27**:1126-1131, 1942.

6. Kinsey, V. E., and Grant, W. M.: The Mechanism of Aqueous Humor Formation Inferred from Chemical Studies on Blood-Aqueous Humor Dynamics, J. Gen. Physiol. **26**:131-149, 1942.

7. Kinsey, V. E., and Bárány, E.: The Rate of Flow of Aqueous Humor: II. Derivation of Rate of Flow and Its Physiologic Significance, Am. J. Ophth. **32**:189-202 (June, Pt. 2) 1949.

8. Palm, E.: On the Phosphate Exchange Between the Blood and the Eye, Acta ophth., Supp. 32, 1948.

9. Ross, E. J.: Circulation of the Aqueous Humour and the Experimental Determination of Its Rate of Flow, Brit. J. Ophth. **36**:41-51, 1952.

10. Davson, H., and Matchett, P. A.: The Control of the Intraocular Pressure in the Rabbit, J. Physiol. **113**:387-397, 1951.

11. Uribe y Troncoso, M.: The Intrascleral Vascular Plexus and Its Relation to the Aqueous Outflow, Am. J. Ophth. **25**:1153-1162, 1942.

12. Goldmann, H.: Über das Fluorescein in der menschlichen Vorderkammer: Das Kammerwasserminutenvolumen des Menschen, Ophthalmologica **119**:65-95, 1950.

13. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204-214, 1950.

14. Grant, W. M.: Clinical Measurement of Aqueous Outflow, Arch. Ophth. **46**:113-131, 1951.

15. Ascher, K. W.: The Aqueous Veins: Physiologic Importance of the Visible Elimination of Intraocular Fluid, Am. J. Ophth. **25**:1174-1209, 1942.

16. Zeller, K.: Studien an Bindehautgefässen, Klin. Monatsbl. Augenh. **66**:613, 1921.

17. de Vries, S.: De zichtbare afvoer van het kamerwater, Amsterdam, Drukkerij Kinsbergen, 1947.

18. Stepanik, J.: Measuring Velocity of Flow in Aqueous Veins, Am. J. Ophth., to be published.

19. Ascher, K. W.: Aqueous Veins and Their Significance for Pathogenesis of Glaucoma, Arch. Ophth. **42**:66-76, 1949.

20. Ascher, K. W., and Spurgeon, W. M.: Compression Tests on Aqueous Veins of Glaucomatous Eyes, Am. J. Ophth. **32**:239-251 (June, Pt. 2) 1949.

21. Kronfeld, P.: Tonography, A. M. A. Arch. Ophth. **48**:393-404, 1952.

22. Henderson, T.: Tr. Ophth. Soc. U. Kingdom **128**:47, 1908.

23. Maggiore, L.: Struttura, comportamento e significato del canale di Schlemm nell'umano, in condizioni normali e patologiche, Ann. ottal. e clin. ocul. **40**:317-462, 1917.

24. Dvorak-Theobald, G.: Schlemm's Canal: Its Anastomosis and Anatomic Relations, Tr. Am. Ophth. Soc. **32**:574, 1934.

25. Ashton, N.: Anatomical Study of Schlemm's Canal and Aqueous Veins by Means of Neoprene Casts: II. Aqueous Veins (cont.), Brit. J. Ophth. **36**:265-267, 1952.

FIBRIN FILM TREATMENT OF CORNEAL DISEASES

C. W. WEISSER, M.D.
PITTSBURGH

WE CONSTANTLY search for new or improved medication which will relieve pain and speed healing. In treating corneal diseases we often partially defeat one purpose to accomplish another. Some of our commonly used agents, for example, tetracaine and hydrous wool fat U. S. P. (lanolin), while relieving pain or serving as a vehicle, may delay corneal healing. If we can find an agent which both relieves pain and stimulates or supports healing, we shall come close to an ideal medicine for treating corneal disease. In thromboplastin we have such an agent. When properly used, it relieves pain quickly and permits rapid replacement of corneal epithelium. My colleagues and I have used it in the treatment of about 100 corneal lesions of various types, with very satisfying clinical results. We have also attempted to verify the work in laboratory animals, with some encouraging and stimulating experiments.

The material we used in all this work was a combination of two biologicals which have been previously used for other purposes: thrombin U. S. P.,* 5,000 units, and normal human plasma U. S. P.,† 2.5 cc.

The result of instilling a drop of each of these agents onto the cornea is a clot of fibrin film, which under normal circumstances covers the damaged area, relieves pain, and permits rapid healing even in an unpatched eye. This is the same substance used in plastic surgery, neurosurgery, and ophthalmic surgery. Tassman has aptly called it physiologic glue. Brown and Nantz stated that it is an adhesive, and not a healing agent, but by this very characteristic it allows more rapid replacement of epithelium than otherwise occurs. Adler has demonstrated that regenerating epithelial cells adhere more firmly to each other than to the underlying tissue. Friedenwald has proved that epithelium can migrate as well as regenerate. If a good adhesive substance is available, the cells can better adhere to the injured area by both migration and regeneration. Arno Town has advocated the use of thromboplastin in treatment of chronic corneal conditions where interruption of the epithelium causes edema of the cornea, as ably shown by the excellent works of Cogan.

For the past two years this fibrin film has been used in our private practice in the cases briefly summarized in Table 1.

Table 1, because of the use of averages, cannot tell the story adequately. To illustrate better some of the particular benefits of this treatment, a few cases are abstracted.

Read before the Section on Ophthalmology at the 102nd Annual Meeting of the American Medical Association, New York, June 4, 1953.

* Parke, Davis & Company, Thrombin Topical (bovine origin), 5 cc.

† Sharp & Dohme, Inc., Lyovac Normal Human Plasma.

Case 1.—A chemist who splashed hot perchloric acid into both eyes began fibrin film treatment within an hour—only one eye was patched. He never lost a day's work and was free of pain within a few hours. Neither cornea stained after four days, and his vision remains 20/20 in each eye.

Case 2.—A nurse had recurrent erosion of the cornea following a fingernail scratch. Four previous attacks had kept her from duty for five days each. When examined, she could not

Table 1.—*Clinical Results*

Type of Disease	Average Time Before Treatment Was Started	Permanent Relief of Pain	Average Healing Time	Final Vision
18 Fingernail scratches	42 hr.	8 hr.	40 hr.	20/20 (15) 20/70 (3)
20 Miscellaneous abrasions	53 hr.	7 hr.	38 hr.	20/20 (16) 20/70 (4)
12 Chemical burns	5 10 hr. 7 4 days	4 hr. 10 hr.	85 hr. 10 days	20/20 (10) 20/30 (2)
10 Industrial burns	37 hr.	2 hr.	24 hr.	20/20 (10)
15 Ulcers	3 days	8 hr.	32 hr.	20/20 (12) 20/40 (2) 20/200 (1)
9 Chronic keratitis	5 yr.	Immediate to 6 days		?
9 Acute keratitis	36 hr.	5 hr.	36 hr.	20/20 (9)
5 Failures	3 days	4+ days	6+ days	20/20 (3) 20/40 (2)

Table 2.—*Experimental Results*

Experiment No.	No. of Rabbits (or Rats)	Abrader	Average Healing Time	
			Treated Eye	Untreated Eye
1	1	Needles	15	33
2	3	Sandpaper	32	65
9	6	20% HNO_3	50	64
10	6 rats	Mechanical abrader	28	49
11	6	Square superficial keratectomy	45	48
12	5 rats	2 mm. trephine (superficial keratectomy	28	36
13	6	2 mm. trephine (superficial keratectomy)	27	Calsulfhydryl * 55
20	6	Monel Applicator HNO_3	58	86
21	5 rats	Monel Applicator HNO_3	54	Tetracaine 92
28	6	HNO_3 filter paper	62	Calsulfhydryl * 96
30	6	5 mm. trephine	36	86
35	6	5 mm. trephine	48	Chlortetracycline ointment 92

* Hydrosulphosol.

tolerate the slightest light or opening of her eye. After 2 drops she was comfortable, and she was on duty the next day, with no staining of her cornea with fluorescein.

Case 3.—A Moorens ulcer had been treated for three months, gradually progressing despite local and parenteral use of antibiotics and almost every known local treatment. Within a day after starting of fibrin film, her eye was comfortable, and the ulcer completely healed in two weeks.

Case 4.—A debilitated girl had a severe dendritic ulcer for two weeks, requiring tetracaine every 15 minutes, without complete relief of pain. She could not sleep. She was comfortable in about 30 hours after starting treatment, and the cornea did not stain after 48 hours.

Many less severe cases had even more spectacular results. Antibiotics and tetracaine may be added to thromboplastin if desired, without affecting either the clinical or the laboratory results, and may prove to enhance the therapeutic benefit.

A brief summary of the animal work shows an encouraging picture (Table *2*).

The figures in Table *2* are, again, averages. Some of our animal work was very inconclusive, owing to difficulties in technique, time, animal deaths, or unknown reasons; but frequently the healing time was less than, or at least as good as, that in the fibrin-film-treated eye. The eyes treated with other agents often had more secretion and sometimes went on to perforation.

We did only one histopathologic study. A treated animal died, and the thrombin-plasma-treated eye, which had seemed worse clinically, proved to be exceedingly normal, with regenerating epithelium and almost normal stroma. The untreated eye had only a few cells left in the stroma, very little epithelial regeneration, and much pus and edema.

Some of our experiments, which were carried out through the Industrial Hygiene Foundation at the Mellon Institute of Industrial Research, were inconclusive because of laboratory difficulties, but Table *2* shows that fibrin film compares favorably with other treatment.

In summary, we have in the fibrin film therapy an encouraging aid to rapid healing and relief of pain in even the severest corneal lesions. It may be combined with antibiotics or anesthetics. The eyes seldom need be patched. It can be speculated that the fibrin film contains antibodies of some value in treating ulcers and other infections.

ABSTRACT OF DISCUSSION

Dr. Derrick Vail, Chicago: In discussing Dr. Weisser's paper, one is impressed with the sincerity of his work and his presentation, and with the spectacular nature of some of his cases, cases concerned with the questions of rapidity of healing and the relief of pain that has bothered us all for many years.

I find myself in somewhat of a dilemma in discussing this paper, for if we accept it as a preliminary report and as a suggestive mode of treatment that should be tried, I think it is all right. But I should be unhappy to accept it as a definitive paper, one that is dogmatic, which it is not.

The paper that I received from Dr. Weisser was actually an abstract of a paper which, in my opinion, does not fulfill the requirements of a scientific presentation. I do not say this in a critical sense, but I do say that it handicaps me in being fair to Dr. Weisser and his work, which I think is very important and stimulating.

I am unhappy about it for the same reason that he is—that his laboratory work was handicapped by the conditions in which he found himself and over which he had no control.

While the figures for the difference between the treated eye and the untreated eye are somewhat impressive, it would have made me much happier if he had fulfilled the scientific criteria of experimental work in producing a standard lesion and then following it through with histologic studies at various periods of observation, for example, as Dr. Swan did in the work he has just so ably presented.

It is not possible for all of us to have the laboratory facilities of some of our colleagues, and I say this in no sense in disparagement of Dr. Weisser. As a matter of fact, I admire him for attempting to do experimental studies under conditions that are not very satisfactory.

I find it difficult to evaluate the clinical value of any preparation instilled into the eye. We all have the same experience. In fact, some of us are overenthusiastic in our belief that some preparation, such as this one, will do such and such a thing

in a remarkably short time. We have seen the enthusiasm of some people in the application of certain solutions for burns and injuries which has not been substantiated by the course of time, or as yet by experimental proof.

Theoretically, in the use of the fibrin film combination, Dr. Weisser has a substance which is physiologically sound. It covers the injured surface. It spares the denuded nerves and membrane from exposure, and it produces a sticky substance that should, and probably does, promote healing. I think the work is significant enough to require further studies and observation by all of us.

The whole story of the fibrin film and the physiologic glue is a fascinating one. In 1943 I returned from overseas, and, among the other work I had to do for the Army, it was my thought to see whether there was anything for ophthalmology in the blood fractionations that Professor Coen, of Harvard, had discovered. I had in mind the use of a fibrin film of tenacious material to prevent the formation of symblepharon and for the plugging of scleral wounds in soldiers. I was informed by Professor Coen that Dr. Terry had already seized upon this idea and had been working on the problem. On my talking it over with him, Terry discouraged me because he felt that the method was producing injuries through toxic reactions in the eyes, and for that reason he had abandoned his research.

I shall leave it to Dr. Tassman, Brown, Vance, or Town to describe the work they have done. I am much impressed with Dr. Tassman's studies and experimental work whereby the use of this fibrin glue has promoted definite healing.

Dr. Isaac Tassman, Philadelphia: I should like to enlarge a little on the application of this preparation in the treatment of corneal conditions. Dr. Weisser, as he stated, has obtained very satisfactory results in the treatment of various corneal lesions with this preparation.

My colleagues and I first began using the plasma and thrombin in corneal conditions about 1946, and we were able to demonstrate, both experimentally and clinically, the adhesive and sealing properties of the fibrin film. It is necessary to apply only one or two drops to the end of a wisp of cotton or a glass slide, and in five minutes or so the cotton can be removed only by tearing it away; it does, therefore, actually provide adhesion and sealing.

In the last six years we also have been using this preparation as an adjunct in the treatment of certain corneal conditions, principally those enumerated by Dr. Weisser, not so much for the purpose of providing healing as to furnish a protective covering when it is desired after the usual or conventional forms of treatment have failed or when it is desired to prevent exposure to the air. In such cases it is possible to eliminate the need for a patch over the eye and to protect the cornea from the patient's rubbing the eyelids.

Dr. Weisser stated that he uses the Sharp & Dohme preparation of Lyovac, which does provide twice the concentration of fibrinogen that normally occurs in the blood. He also employs the Parke, Davis & Company preparation of thrombin, which is put into solution. This is supplied by Parke, Davis & Company in a 5 cc. vial containing 5,000 units, a great deal of which might be wasted.

We employ the Upjohn preparation of thrombin, which is supplied in vials containing 1,000 units of the dried thrombin, which, when put into solution with 1 cc. of the diluent, isotonic saline, gives us 1,000 units per cubic centimeter.

I have learned that Parke, Davis & Company now has a preparation of 1,000 units which is put out in a smaller vial, and which might be used to better advantage and with less chance for waste.

I should like to emphasize also that when the plasma is first applied in 1 or 2 drops, and then 2 or 3 drops of the thrombin solution is added, it is necessary to keep the eye open for at least three to four minutes if possible, in order to give the mixture an opportunity to dry.

Since the beginning of the year we have found that the addition of 1 drop of methylcellulose will provide more body and consistency to the mixture, as well as additional adherence. The preparation we now use therefore is a 1:2:3 mixture—1 drop of methylcellulose first, 2 drops of the plasma solution, and 3 drops of the

thrombin solution in a concentration of 1,000 units to 1 cc. It takes several minutes for the mixture to dry, but after it does dry it provides a very satisfactory seal or covering for the wound.

We have treated conditions very similar to those enumerated by Dr. Weisser and have found it of value even in the healing of corneal lacerations when there was no gaping or separation of the edges.

[Slide] This is a laceration which healed after being treated only with the application of the thrombin and plasma solutions.

[Slide] This shows a corneal ulcer which had been under treatment in another city for seven months, and which did not respond to treatment. We used the ordinary forms of treatment and finally resorted to the application of the thrombin and plasma solutions, with a drop of methylcellulose. The eye then showed the first signs of healing.

DR. IRVIN LEVY, Trenton, N. J.: Dr. Weisser is to be congratulated on his excellent paper, which represents considerable clinical material. However, I thoroughly agree with Dr. Vail that in order that this treatment may be properly evaluated, controls should have been used and laboratory experimentation should have been done.

About three years ago, when my baby scratched the cornea of my wife's eye, I became interested in the treatment of corneal injuries.

The routine conservative treatment of local anesthesia, patching, and sedation did not control her excruciating pain; and, as you all know, this severe pain is not unusual. After an unsuccessful course of treatment, with only temporary relief of pain, I had the idea of using physiologic glue to cover the denuded area, in the same fashion as Dr. Tassman had used it for his wound closure in cataract surgery.

Since then, I have used plasma and thrombin solutions many times for the treatment of corneal conditions, both as an office and as a hospital procedure. The results have been excellent. By this, I mean that the relief from pain has been remarkable—almost as though a magic word were used.

In order properly to evaluate this treatment, I tried it on rabbits.

On the basis of my experimentation, there is no evidence that the rate of healing is either speeded up or retarded. The details of this laboratory work, as well as the clinical results, will be presented at the next annual Wills Hospital conference.

The disadvantages of this procedure are the length of time necessary to carry out the treatment properly and the cost of the materials.

The plasma and thrombin solutions must be freshly prepared and used on the same day.

It is my opinion that this treatment will frequently be unsuccessful if it is not carried out with meticulous detail.

The technique that I have found to be most satisfactory is as follows:

1. The patient is placed in the reclining position.

2. Several instillations of a local anesthetic are made into the conjunctival sac. I prefer to use 4% cocaine. Of course, there will be many who will object to cocaine and will prefer some other anesthetic, such as tetracaine, butacaine, or phenacaine. However, I personally use cocaine, not only because I feel it is the best anesthetic but also because it has a slight drying effect on the corneal epithelium which I feel is advantageous in this type of procedure.

3. Excessive illumination on the affected eye is unnecessary and should be avoided.

4. Whenever possible, the unaffected eye should be covered by a light patch.

5. After the affected eye is satisfactorily anesthetized, a speculum is inserted into the conjunctival sac.

6. The patient is then asked to fix in such a fashion that the denuded corneal area will not be touched by the lids.

7. The conjunctival sac is irrigated well with an antiseptic solution. In cases of this kind, my preference is a freshly made penicillin solution of 5,000 units per cubic centimeter.

8. Small pieces of absorbent cotton are placed in the upper and lower cul-de-sacs to absorb the tears and keep the operative field dry.

9. The corneal area is dried thoroughly with an applicator and the affected corneal area cauterized as indicated.

10. A drop or two of plasma solution is then placed on the affected corneal area.

11. Immediately thereafter, a drop or two of thrombin solution is placed on the plasma solution.

12. Then, with a fine hypodermic needle the plasma and thrombin mixture is gently stirred for just a fraction of a second.

13. A gentle stream of warm dry air is then directed on the cornea to promote drying of the plasma and thrombin mixture. For this I use an ordinary flush bottle syringe. In order to obtain warm dry air, I light a Bunsen burner and, holding the syringe above the flame, aspirate warm dry air into the syringe.

14. When the coagulum is dry and firm, which usually occurs in three to five minutes, any strands between the corneal area and the palpebral conjunctiva are gently severed. I never grasp these strands with forceps, but just cut these strands with a sharp scissors; I definitely do not pull the coagulum.

15. When the coagulum is entirely dry, I carefully remove the speculum and the cotton from the cul-de-sac, so that the coagulum is not disturbed.

16. Both eyes are gently closed, making sure that the lids of the treated eye do not rub on the coagulum.

17. While the eye is closed, a similar mixture of the plasma and thrombin solutions is then applied to the lashes in order to glue the eye shut.

18. When this solution is dry and has formed a firm coagulum, the affected eye is covered with a light pressure dressing. The eye is dressed in 48 hours, or sooner if indicated. Then, if there is any stain or the eye is painful, plasma solution and thrombin solution is reapplied. No ointment is used in the eye.

19. The dressing may be removed any time after the second day, or as soon as there is no more staining.

I am sure that if you follow this technique you will realize that the plasma and thrombin treatment has given us a real aid in the treatment of corneal injuries.

Dr. Harvey Thorpe, Pittsburgh: I have had some personal experience with the use of Lyovac and thrombin in the treatment of ulcerative keratitis and also in the management of a few cases of epidemic keratoconjunctivitis. It has been of definite benefit in one-third of my cases with chronic ulcerative keratitis.

Dr. C. William Weisser, Pittsburgh: I want to thank Dr. Vail for his very justified criticism of the text of the paper. I found it very difficult to write a 15-minute paper and include all I wanted to say. It was my hope merely to present this report so that those of you who are interested might use this material in your severe cases.

I do not think the method should be used indiscriminately in every case that comes along, for it is inconvenient and expensive.

PHASIC VARIATIONS IN TONOGRAPHY

HARRY HORWICH, M.D.
AND
GOODWIN M. BREININ, M.D.
NEW YORK

IN THE Proctor Lecture of 1951, Duke-Elder [1] described three main types of phasic variation of the intraocular tension in simple glaucoma. These were, first, the falling type of curve, occurring in 20% of cases, in which the tension was highest early in the morning; second, the rising type, occurring in 25% of cases, in which the tension was highest in the late afternoon, and, third, the double variation, or biphasic type, occurring in 55% of cases, in which there were two peaks, one in the forenoon and the other in the late afternoon. He noted that simple glaucoma was a state "characterized initially by an instability of the ocular tension which shows a diurnal phasic variation of more than 5.0 mm. Hg."

Grant,[2] in 1950, described his technique for tonography in detail and discussed its theory and application. As he stated, his work was based on the calculations published by Friedenwald [4] on the relationship between changes in ocular volume and Schiøtz scale readings. The following year Grant [3] amplified the depth and clinical scope of his work and derived a second set of normal values for the facility of aqueous outflow and the net rate of flow (Table 1).

Other early pioneers in this field were Moses and Bruno,[5] who used a technique similar to that of Grant. More recently, de Roetth and Knighton,[6] and then Kronfeld,[7] have published their findings in tonographic studies and have offered other values for normal outflow. In Europe, Prijot and Weekers, having done considerable work on normal [8] and glaucomatous [9] eyes, have come to the same conclusion regarding the diminished facility of aqueous outflow in chronic simple glaucoma.

Although all work published to date agrees that there is diminished aqueous outflow in chronic simple glaucoma, very little more has been discovered about this abnormal condition. Ascher [10] pointed this out clearly when he stated that though resistance to outflow is present, the exact site is not known; i. e., whether it is in the trabeculum, Schlemm's canal, the aqueous veins, or the recipient vessels. Moreover, it is not known whether the disturbance is anatomical or functional or both.

PRESENT INVESTIGATION

Our purpose in the present study was to investigate phasic variations in chronic simple glaucoma by the tonographic method. Tonography permits a quantitative analysis of the aqueous outflow and provides more useful information than simple

From the Department of Ophthalmology, New York University Postgraduate Medical School of Medicine.

tonometry and bulbar compression tests. In addition, we have tried to countercheck the diagnostic reliability of tonography, especially to see whether diurnal variations might produce misleading findings. Such a possibility is of considerable importance because of the enthusiasm with which tonography has been greeted and the great reliance that has been placed upon it.

METHOD

In general, we have used the technique described by Grant. However, we have availed ourselves of the many practical hints and useful charts in the booklet by Ballantine and Johnson [11] on tonographic technique. We did not use an automatic recording device.

The patients were selected in the following manner: All were patients from the glaucoma clinic. In each case the diagnosis of chronic simple glaucoma was made on the basis of increased intraocular tension plus one of the following: glaucomatous visual field defect, a positive water-ingestion provocative test, or glaucomatous cupping. No patient had any history of acute congestive glaucoma or evidence of secondary glaucoma. All eyes were gonioscoped and found to be of the open-angle type. None of the eyes had ever been operated on for any condition. Case 20 had a record for only one eye, since the other had gone on to absolute glaucoma. All use of eye drops was discontinued for at least 24, and usually 48, hours preceding the time of testing. This was because we had come to feel that in some cases the effect of the miotic did not wear off in 24 hours. In fact, we have seen several cases in which the effects of the miotic on chronic simple glaucoma did not wear off for two weeks.

TABLE 1.—*Normal Values for Aqueous Flow*

	Normal C	Normal K	Average C	Average K
Grant,[3] 1950	0.15-0.34	2.3-5.4	0.243	3.66
Grant,[3] 1951	0.11-0.44	1.1-5.13	0.22	2.4
de Roetth and Knighton [5]	0.10-0.52	1.0-9.3	0.244	4.0
Kronfeld	0.14-0.44	.....	0.24	....

The patients were admitted to the hospital. The testing was done with the patient supine, the neck unconstricted, and fixation in the primary position. A Müller electronic tonometer was used. It was kept satisfactorily friction-free by frequent polishing of the plunger and the inside of the barrel with an automobile polish containing silicone. No automatic recording device was available; so values were simply read from the tonometer dial. After topical anesthesia with 1% tetracaine hydrochloride, the freshly adjusted tonometer was placed vertically on the cornea for five to six minutes. The lids were held away from the globe with the fingers of the opposite hand so that no pressure was exerted on the globe, and all preliminary massaging movements were avoided. In this manner, the tonometer needle could be seen to swing freely with the transmitted vascular and respiratory pulsations. An average value was interpolated between the extremes of each swing, the figures being checked every 10 to 15 seconds. The readings taken from these figures were for four-minute periods, starting when the needle showed the initial instability had been overcome. These readings were taken in both eyes at approximately 7 a. m., 12 noon, 5 p. m., and 10 p. m., i. e., roughly at five-hour intervals during the waking period. All readings were taken by the same observer.

RESULTS

Table 2 shows the values found for C, the facility of aqueous outflow; K, the net rate of flow; and P_0, the original pressure or the Schiøtz equivalent. There are 39 eyes, in 20 patients. Each of the values is plotted for four diurnal readings.

Chart 1 is a scattergram, which was composed with the values for C as the ordinates and P_0 as the abscissas. This was found to be appropriately L-shaped; that is, impaired outflows were usually associated with high tensions, and normal outflows were usually associated with normal tensions.

TABLE 2.—*Variations in Aqueous Outflow and in Tension in Twenty Patients with Chronic Simple Glaucoma*

Patient		C		K		P_a	
		O. D.	O. S.	O. D.	O. S.	O. D.	O. S.
1	7	0.06	0.04	1.31	1.47	21.9	46.7
	12	0.07	0.01	1.61	0.56	23.1	35.9
	5	0.10	0.01	1.95	0.66	19.5	66.4
	10	0.07	0.02	1.17	1.08	16.8	53.9
2	7	0.15	0.11	2.64	2.80	25.2	26.0
	12	0.00	0.02	0.00	0.67	48.9	33.7
	5	0.01	0.04	0.41	1.14	41.7	28.7
	10	0.03	0.04	1.20	1.20	40.4	30.0
3	7	0.01	0.05	0.21	1.66	21.4	33.2
	12	0.03	0.10	0.53	3.09	17.6	30.9
	5	0.02	0.03	0.36	0.88	18.2	29.4
	10	0.08	0.04	1.33	0.70	16.7	17.6
4	7	0.04	0.03	1.20	0.95	30.1	31.7
	12	0.05	0.06	1.56	1.90	31.2	31.7
	5	0.05	0.08	1.50	2.28	30.1	28.6
	10	0.07	0.13	1.23	2.69	17.6	20.7
5	7	0.05	0.08	1.42	1.45	28.4	18.2
	12	0.04	0.07	0.92	1.40	23.1	20.6
	5	0.12	0.11	2.22	2.40	18.5	21.9
	10	0.05	0.07	1.42	1.91	28.4	27.3
6	7	0.09	0.06	1.22	0.70	13.6	11.7
	12	0.09	0.09	1.66	1.19	18.4	13.2
	5	0.07	0.11	1.23	1.58	17.6	14.4
	10	0.17	0.14	2.24	1.51	13.2	10.8
7	7	0.09	0.06	1.33	1.06	14.8	17.7
	12	0.11	0.09	1.30	1.45	11.9	16.2
	5	0.09	0.02	0.96	0.22	10.7	11.1
	10	0.09	0.10	2.71	1.43	30.2	14.3
8	7	0.08	0.07	1.54	1.31	19.3	18.8
	12	0.11	0.07	2.00	1.20	18.2	17.2
	5	0.07	0.07	1.07	1.13	15.4	16.2
	10	0.11	0.12	2.28	2.17	20.8	18.1
9	7	0.13	0.03	2.36	1.83	18.2	61.1
	12	0.09	0.04	1.21	1.44	13.5	36.0
	5	0.09	0.04	1.42	1.20	15.8	30.0
	10	0.08	0.03	1.15	0.72	14.4	24.1
10	7	0.08	0.20	2.27	3.24	28.4	16.2
	12	0.04	0.14	1.52	2.40	38.0	17.2
	5	0.08	0.24	2.27	3.43	28.4	14.3
	10	0.18	0.20	4.71	2.86	26.2	14.3
11	7	0.07	0.07	1.98	1.98	28.4	28.4
	12	0.15	0.14	4.81	4.31	32.1	30.8
	5	0.00	0.00	0.00	0.00	38.0	38.0
	10	0.18	0.15	5.77	4.26	32.1	28.4
12	7	0.07	0.00	3.47	0.00	49.6	61.0
	12	0.01	0.01	0.30	0.55	30.8	55.3
	5	0.20	0.03	9.36	1.53	46.8	51.5
	10	0.16	0.02	3.32	0.61	20.8	30.8
13	7	0.04	0.13	2.48	2.34	62.1	18.0
	12	0.04	0.07	1.98	1.03	49.6	14.8
	5	0.01	0.11	0.37	2.20	37.6	20.0
	10	0.09	0.11	0.00	1.22	34.9	11.1
14	7	0.09	0.15	1.42	2.44	15.8	16.3
	12	0.13	0.22	1.92	3.56	14.8	16.2
	5	0.22	0.04	4.24	0.59	19.3	14.8
	10	0.15	0.13	2.37	1.84	15.8	14.2
15	7	0.05	0.06	0.96	0.92	19.3	15.4
	12	0.05	0.04	1.15	0.83	23.1	20.8
	5	0.06	0.08	1.24	1.41	20.8	17.7
	10	0.11	0.09	1.94	1.26	17.7	14.0
16	7	0.08	0.10	2.28	1.43	28.6	14.3
	12	0.05	0.12	1.69	1.77	33.9	14.8
	5	0.05	0.07	2.23	1.66	44.7	23.7
	10	0.02	0.07	0.78	1.24	38.9	17.7
17	7	0.15	0.07	3.25	1.48	25.0	21.2
	12	0.08	0.07	1.54	1.29	19.3	18.5
	5	0.07	0.05	1.45	0.90	20.8	18.0
	10	0.10	0.12	1.62	2.06	16.2	17.2
18	7	0.08	0.14	2.00	2.41	25.0	17.2
	12	0.10	0.04	0.28	1.12	28.4	28.4
	5	0.05	0.15	1.36	2.22	27.3	14.8
	10	0.10	0.20	2.24	2.74	22.4	13.6
19	7	0.10	0.13	1.66	2.15	16.6	15.9
	12	0.18	0.11	1.72	1.49	16.0	13.6
	5	0.15	0.13	3.46	2.60	23.1	20.0
	10	0.12	0.13	1.94	2.10	16.2	15.9
20	7	0.02	Absent	0.31	Absent	34.9	Absent
	12	0.00	Absent	0.00	Absent	41.7	Absent
	5	0.00	Absent	0.00	Absent	41.7	Absent
	10	0.02	Absent	0.38	Absent	41.7	Absent

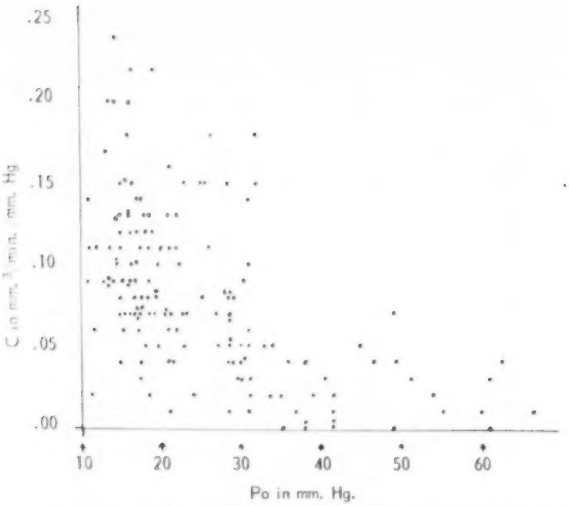


Chart 1.—Scattergram to show relationship between intraocular tension and coefficient of facility of aqueous outflow. Each spot represents the intraocular tension at the beginning of a tonographic record plotted against the value of that record.

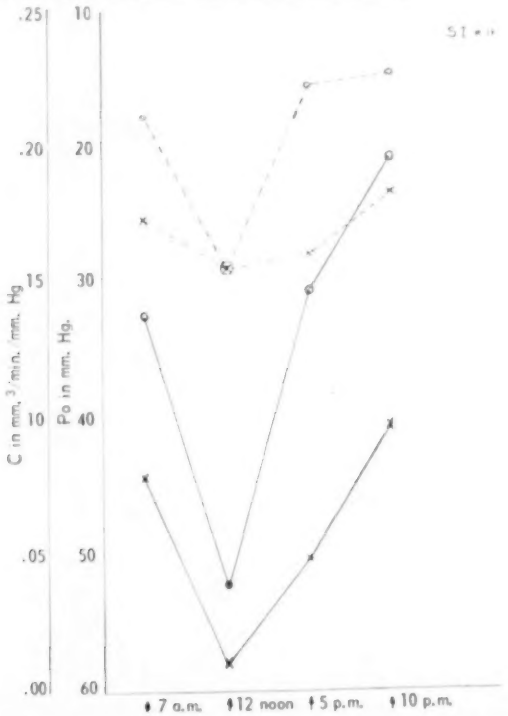


Chart 2.—Correlated type of curve. The x's are values for the right eye, and the o's values for the left eye. Solid lines represent values for C; dotted lines represent values for P_o. It is seen that as C grows numerically smaller, P_o grows numerically larger, and vice versa.

Each case, then, had its values for C and P_0 plotted as ordinates on an individual graph, with time plotted as the abscissas, as in Charts 2 and 3. This established the type of diurnal curve, according to the classification of Duke-Elder, and showed whether there was any relation between the phasic variations in tension and variations in outflow. In this small group of 39 eyes, there were 14 curves of the double, or biphasic, type, 13 of the rising type, and 12 of the falling type. However, it is readily seen that with such readings, only four a day, and taken five hours apart, one might easily misclassify some of the curves. This source of error could not be

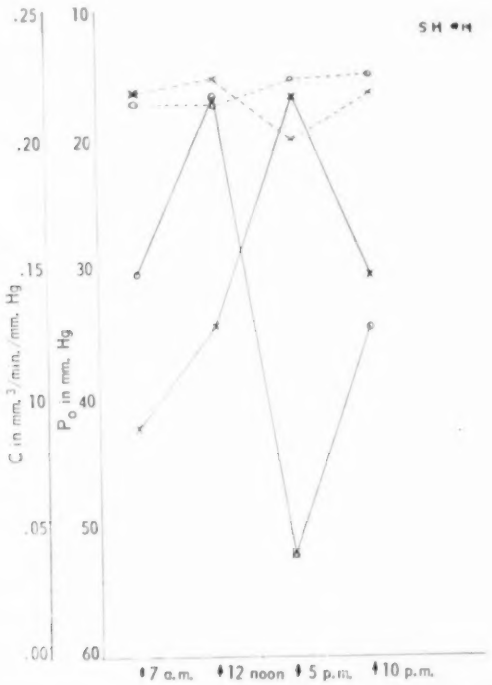


Chart 3.—Uncorrelated type of curve. The x's are values for the right eye, and the o's values for the left eye. Solid lines represent values for C; dotted lines represent values for P_0. It is seen that there is no apparent relationship, inverse or otherwise, between C and P_0.

remedied, as four readings a day reached the tolerance, and in many cases exceeded the tolerance, of the subject.

Variations in outflow were seen to be as marked as variations in tension. In one 24-hour period some patients showed a range from no apparent outflow to normal facility. It may be seen from Table 2 that the highest tension was 66.4 mm. Hg, and the lowest 10.7 mm. Hg; and the lowest value for C was 0.00, and the greatest was 0.24 cu. mm., per minute per millimeter of Hg.

From the individual graphs it was determined that in 23 cases the fluctuations of C varied inversely with those of P_0. We described this type of curve, in which the facility of outflow followed the tension appropriately, a correlated curve. An

example of this is Chart 2. In 16 cases, however, a rise in tension was not associated with a decreased facility of outflow, and a fall in tension was not associated with an increased facility of outflow. This we called an uncorrelated curve, Chart 3 being an example. Of the 23 cases of correlated curves, 5 were of the falling type, 10 of the rising type, and 8 of the biphasic type. Of the 16 cases with uncorrelated curves, 7 were of the falling type, 3 of the rising type, and 6 were biphasic (Table 3).

Although the figures are far too few for statistical analysis, it can be seen that about half the cases of the biphasic type were correlated for C and P_0, that in the falling type they were more frequently uncorrelated, and that in the rising type they were more frequently correlated; that is, of 13 cases showing a rising type of curve, 10 showed C and P_0 to be correlated.

It will be seen from Table 1 that the lowest normal limits for C have been proposed as varying from 0.10 to 0.15 cu. mm. per minute per millimeter of Hg. If the former figure is taken, it will be seen from Table 2 that in 37 of 156 readings we obtained normal values in glaucomatous patients. However, by eliminating one patient (Case 19), we can reduce that figure to 30 out of 156. With the higher value for C, we would have obtained normal values only in 11 of 156 readings in glaucomatous eyes. This is a high index of reliability. It will be noted that at least one reading was found to be abnormal in all cases, even though some of the tensions were rather low.

TABLE 3.—*Relation of C Curve to Phasic Variation P_0 Curve*

	Correlated Group	%	Uncorrelated Group	%
Falling	5	22	7	44
Rising	10	43	3	19
Biphasic	8	35	6	37
Totals	23	100	16	100

It was our impression that some of these low tensions may have been due to continued action of the miotics, even though drops had been discontinued. It has not uncommonly been observed that it may take weeks for the tension to rise again in a controlled case of chronic simple glaucoma after discontinuation of miotics. It is quite possible that this persisting effect may have influenced some of our readings.

An equal number of normal eyes were tested in the same manner, and they were found to have normal tensions, to be within the normal range of diurnal variations, and to have normal tonographic values for the facility of outflow.

COMMENT

The small number of patients in this series is due to the difficulty in finding clear-cut cases of chronic simple glaucoma in which operation has not already been done for advancing visual field defects or unsatisfactory medical control. No statistical conclusions can be drawn, therefore.

The series of cases of correlated type suggest that the rising phase of intraocular tension is somehow accompanied by an impeded outflow of aqueous. The occurrence of the uncorrelated type was unexpected, and we can state nothing concerning the dynamics of either relation.

The fact that a normal facility of aqueous outflow may be recorded in a definitely glaucomatous eye constitutes a qualification of the reliability of a single normal tonographic record. We may, rather, confidently label an eye as glaucomatous which has an abnormally low coefficient of facility of aqueous outflow, but we cannot call an eye normal on the basis of one normal tonographic record. This finding is particularly pertinent to those borderline cases which so frequently try the ophthalmologist. We believe, however, that tonography, repeated so as to eliminate the pitfall of phasic variations, is a reliable diagnostic measure in those doubtful cases in which other tests are inconsistent.

The procedure itself is trying to both the examiner and the patient. Twenty minutes of sustained tonometry in one day make corneal abrasions almost inescapable. In single tonographic tests this is no problem; but in the present series an undesirable degree of corneal abrasion occurred in about half the cases; indeed, five patients refused to complete the investigation because of the discomfort and reaction. The denudation of epithelium is due to small movements of the eye, and to prevent such movements by unphysiologic means, such as general anesthesia or fixation of the globe and tonometer, would be misleading in such an investigation.

We feel that a great deal concerning the dynamics in this disease could be learned from tonography done, say, every 2 hours for 24 hours. However, we have not been able to work out a practical means to accomplish this.

CONCLUSIONS

From such a small series of cases it is difficult to draw conclusions. However, we should like to state some impressions.

1. The rising phase of ocular tension is usually accompanied by a decrease in the facility of aqueous outflow.

2. In cases in which other tests are equivocal, tonographic phase variation studies are of help in establishing the diagnosis of chronic simple glaucoma.

3. A single normal tonographic record does not necessarily rule out glaucoma.

4. Phasic tonography should be reserved for diagnostic problems because of the likelihood of corneal abrasion.

5. It is generally assumed that the high tension occurring in chronic simple glaucoma is due to impaired aqueous outflow. Therefore one might conclude that there is a direct simple relationship between the two. The large percentage of cases in this series which showed uncorrelated curves implies that the relationship is not a simple one, and that probably other mechanisms are involved.

6. If a single tonographic record is negative in suspected glaucoma, it might be well to repeat the reading at a different time of day, to rule out a misleading phasic variation.

REFERENCES

1. Duke-Elder, S.: The Phasic Variations in the Ocular Tension in Primary Glaucoma, Am. J. Ophth. **35**:1-21 (Jan.) 1952.

2. Grant, W.: Tonographic Method for Measuring the Facility-Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204-214 (Aug.) 1950.

3. Grant, W. M.: Clinical Measurements of Aqueous Outflow, A. M. A. Arch. Ophth. **46**:113-131 (Aug.) 1951.

4. Friedenwald, J. S.: Some Problems in the Diagnosis and Treatment of Glaucoma, Am. J. Ophth. **33**:1523-1538 (Oct.) 1950.

5. Moses, R. A., and Bruno, M.: Rate of Outflow of Fluid from the Eye Under Increased Pressure, Am. J. Ophth. **33**:389-397 (March) 1950.

6. de Roetth, A. J., Jr., and Knighton, W. S.: Clinical Evaluation of the Aqueous Flow Test, A. M. A. Arch Ophth. **48**:148-154 (Aug.) 1952.

7. Kronfeld, P. C.: Tonography, A. M. A. Arch Ophth. **48**:393-404 (Oct.) 1952.

8. Prijot, E., and Weekers, R.: Tonographic Measurement of the Resistance to Aqueous Outflow in Normal Human Eyes, Ophthalmologica **123**:1 (Jan.) 1952.

9. Weekers, R., and Prijot, E.: Tonographic Measurement of the Resistance to Aqueous Outflow in Glaucomatous Eyes, Ophthalmologica **123**:114-112 (Feb.) 1952.

10. Ascher, K. W.: Aqueous Veins: Their Status Eleven Years After Their Detention, A. M. A. Arch. Ophth. **49**:438-451 (April) 1953.

11. Ballantine, E. J., and Johnson, Lorand V.: Tonographic Technique, Cleveland, 1952.

CLINICAL EVALUATION OF THE RODENSTOCK REFRACTOMETER

R. TULLY BRADFORD, M.D.
CINCINNATI
AND
LAWRENCE J. LAWSON Jr., M.D.
CHICAGO

IN THE PAST there have been numerous attempts to design a refractometer which would simplify the objective determination of the ocular refraction. Previously designed metering devices have offered speed of examination, but they have not attained the accuracy of good retinoscopy. The most recent machine is the Rodenstock refractometer (Fig. 1), which is founded on the principles set forth by Schmidt-Rimpler in 1877. An illuminated test plate is placed at the principal focus of a convex lens placed before the eye, so that parallel rays enter the eye and in emmetropia come to a sharp focus on the retina. From this sharp retinal image, parallel rays emerge from the emmetropic eye and are focused by the convex lens in the manner of indirect ophthalmoscopy at the position of the test plate. In myopia the test plate must be moved closer to the convex lens to obtain a clear retinal image, and in hyperopia the test plate must be moved farther out. Therefore the position of the test plate which renders a clear retinal image in relation to the principal focus of the condensing lens measures the far point, or refractive status, of the eye. It is the purpose of this report to evaluate the Rodenstock refractometer by comparing this method with retinoscopy and with subjective cycloplegic refraction.

MATERIALS AND METHODS

In the refractometer, a test plate is transilluminated and light is projected through a porro or inverting prism to form an image of the test figure. By turning the setscrew, a spindle mechanism moves the porro prism, thereby shifting the image along the optical axis of an optometer lens until the image is sharply focused on the retina. Rays of light then leave the retina and are focused by the eye at its far point. This image formed at the far point can be seen by looking through a telescope incorporated in the instrument, and the movement is synchronized with that of the test figure. The end-point of focusing is obtained by observation of the minimum separation of parallel lines on the test-plate image. Freedom from corneal and lenticular reflexes, movement of the test plate, and metering are all accomplished by an ingenious optical system of lenses and prisms housed in the Rodenstock refractometer.

In operation, the setscrew is turned until the test-plate image (Fig. 2) becomes partially clear, and the axis of best clarity is selected for Meridian I. The screw is then turned slowly until the parallel lines below the curves are brought into sharp focus with the greatest plus

Presented before the Chicago Ophthalmological Society, May 18, 1953.

From the Department of Ophthalmology, Illinois Eye and Ear Infirmary of the University of Illinois College of Medicine.

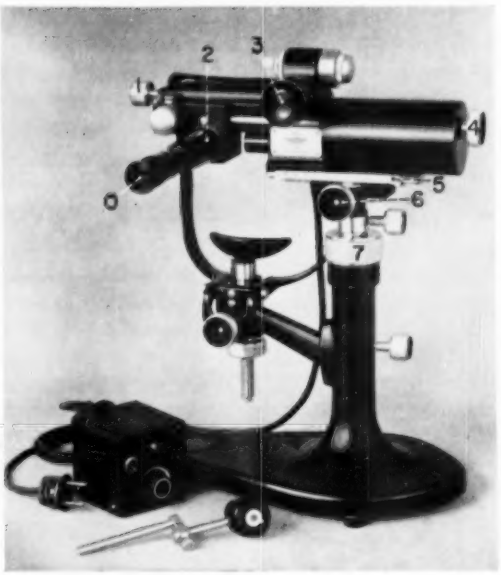


Fig. 1.—The Rodenstock refractometer. *O* indicates ocular; *1*, screw for setting cylinder axis; *2*, telescope; *3*, magnifying lens for reading the diopter and axis scales; *4*, setting screw for focusing test image; *5*, pupillary distance scale; *6*, screw for horizontal regulation, and *7*, nut for vertical control.

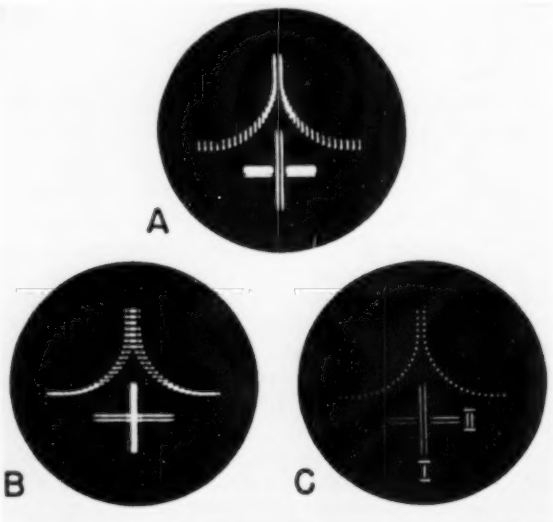


Fig. 2.—*A*, neutralization point for Meridian I in astigmatic eye. In astigmatism dots of test figure appear as short lines. *B*, neutralization point for Meridian II in astigmatic eye. *C*, test figure as it appears at neutralization point in a nonastigmatic eye.

power (Fig. 2*A*). This reading represents the power of the sphere and the axis of any cylinder present. The screw is then turned until Meridian II is brought into focus with the greatest plus power (Fig. 2*B*). The algebraic difference between the readings of Meridian I and Meridian II is the power of the cylinder. All readings on the machine are made with the greatest plus and the least minus power, and the instrument measures refractive error with minus cylinder readings. In a nonastigmatic eye, all elements of the test plate will come into focus simultaneously (Fig. 2*C*).

After a preliminary trial of the instrument in several hundred refractions, a series of 70 patients (140 eyes) was carefully studied by one of us (R. T. B.). Patients ranging from 9 to 38 years of age (average 19 years) with clear media and no ocular pathology were selected. Cycloplegia was produced by the instillation of one drop of 5% homatropine hydrobromide every 10 minutes for five doses, followed by refraction one hour later. Each patient was then examined with a streak retinoscope, utilizing cylinders, with the Rodenstock refractometer, and by subjective refraction under cycloplegia, utilizing trial-case lenses and crossed cylinder. Approximately one week later these patients were reexamined without cycloplegia, using the retinoscope and refractometer. The technique of using the refractometer followed precisely the directions of the manufacturer.

The results obtained with the refractometer with and without cycloplegia were compared with the results with retinoscopy with and without cycloplegia and with those of subjective cycloplegic refraction. The last technique was considered the most accurate estimation of the refractive error and afforded a base line for comparison of the objective methods. Small variations in the numbers of patients in various groups were due to the failure of some to return for postcycloplegic examination. The average differences of sphere, cylinder, spherical equivalent, and cylindrical axis among various techniques for the same eye were calculated individually, and the standard deviations of these differences were obtained.

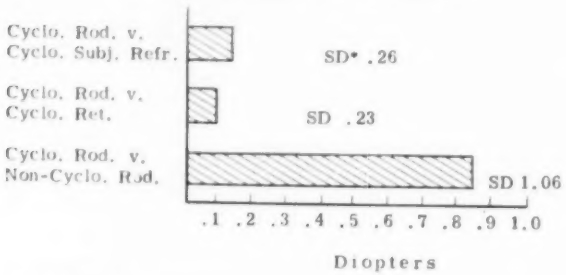
RESULTS

In Figure 3*A* to *D* is shown a comparison of the various techniques under cycloplegia. The Rodenstock refractometer compares favorably with both retinoscopy and subjective cycloplegic refraction. Five eyes presented scissors movements which precluded accurate retinoscopy, but did not interfere with the refractometer readings whatsoever and agreed well with the subjective cycloplegic findings. Rodenstock refractometer determination of the need for a cylinder to correct astigmatic error compared well with the findings by retinoscopy (Fig. 5*A*).

In Figure 4*A* to *D* is shown a comparison of the results with the refractometer and retinoscopy without cycloplegia and the results of subjective cycloplegic refraction. Both the refractometer and the retinoscope showed greater variability of results than did cycloplegic refraction. In 34 eyes (25%), excessive accommodation precluded accurate metering with the refractometer. Only 2 of these 34 eyes could not be retinoscoped satisfactorily. Pupils as small as 1.5 mm. did not interfere with examination by the refractometer, although 6 out of 140 eyes had such small pupils that retinoscopy was impossible. However, pupils less than 1.5 mm. could not be tested well by either method. The detection of an astigmatic error by the Rodenstock instrument compared well with the findings by retinoscopy (Fig. 5).

Other characteristics of the examination with the refractometer were revealed by the preliminary studies on 450 eyes. Head movement could be a very irritating and disturbing factor, and a certain degree of cooperation by the patient was required. The time required for examination with the refractometer was less than

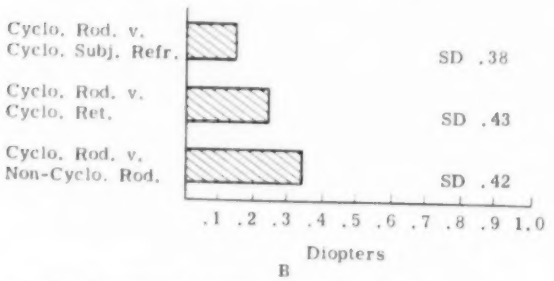
RODENSTOCK REFRACTOMETER WITH CYCLOPLEGIA
AVERAGE DIFFERENCE OF SPHERE



SD = Standard Deviation

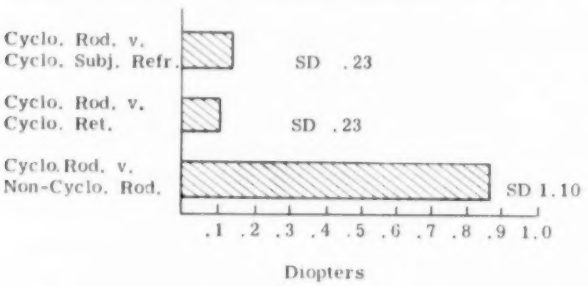
A

AVERAGE DIFFERENCE OF CYLINDER



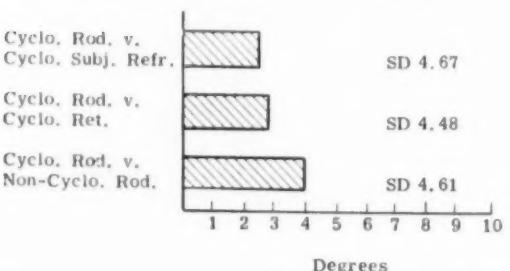
B

AVERAGE DIFFERENCE OF SPHERICAL EQUIVALENT



C

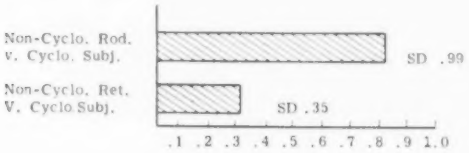
AVERAGE DIFFERENCE OF AXIS



D

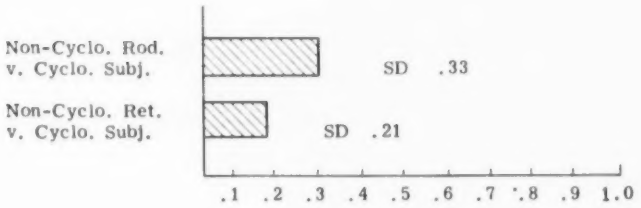
Figure 3.

RODENSTOCK REFRACTOMETER WITHOUT CYCLOPLEGIA: AVERAGE DIFFERENCE OF SPHERE



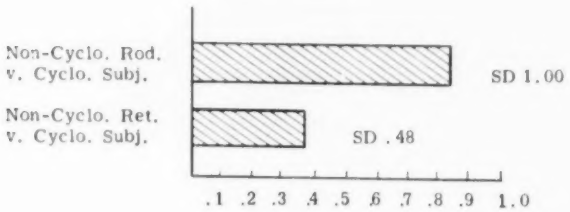
A

AVERAGE DIFFERENCE OF CYLINDER



B Diopters

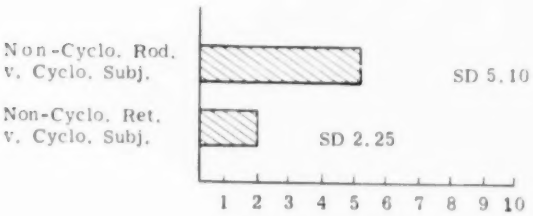
AVERAGE DIFFERENCE OF SPHERICAL EQUIVALENT



Diopters

C

AVERAGE DIFFERENCE OF AXIS



D Degrees

Figure 4.

that required for retinoscopy, although some of this gain was lost when the objective findings were placed in a trial frame and placed in position on the patient. Cloudy media interfered more with refractometer readings than with retinoscopy. Aphakic eyes with clear media gave excellent results with the refractometer. The amount of training and skill necessary to use the refractometer was much less than that required for performing good retinoscopy, and it might be that better results would be obtained with the refractometer than by a relatively poor retinoscopist.

Need for Cylinder as Determined by Retinoscopy vs. Rodenstock Refractometer with Cycloplegia (143 Eyes)

Method	Cylinder	No Cylinder
Retinoscopy	60	83
Rodenstock	57	86

Without Cycloplegia (126 Eyes)		
Method	Cylinder	No Cylinder
Retinoscopy	37	89
Rodenstock	37	89

Figure 5.

CONCLUSIONS

The Rodenstock refractometer seems to be a relatively easy, rapid, and accurate objective means of determining the refractive error under cycloplegia, the results being comparable to those obtained with streak retinoscopy. Without cycloplegia the method is less satisfactory than retinoscopy in many patients because of the large amount of accommodation induced.

Clinical Notes, New Instruments and Techniques

STERILE AIR IN INTRAOCULAR SURGERY

PAUL C. CRAIG, M.D.
READING, PA.

WE HAVE been concerned about the possibility of intraocular infection when injecting air into the anterior chamber. For this reason we have recently developed a simple method of obtaining sterile air. The device consists of a piece of plastic tubing filled at one end with cotton. The tubing has an inside diameter of 3 mm. and is 7 cm. long. It is filled at one end with cotton for a distance of 2 cm. and is then autoclaved.

A syringe with needle or a Noyes irrigator is placed in the open end of the tube as far as it will go, in order to produce an air lock, and it is then filled with air drawn through the sterile cotton. This maneuver is repeated three times so that the possibility of contaminated residual air is excluded. Blood agar cultures subjected to a stream of air from syringe or Noyes irrigator prepared with this method have proved to be sterile.

The fact that we are dealing with sterile air has given us confidence. With peace of mind we have been introducing air into anterior chambers in increasing measure. We feel happy about the air cushion, especially in relation to postoperative flat chambers and the management of anterior vitreous displacement.

232 N. 5th St.

From the Department of Ophthalmology, St. Joseph's Hospital.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

IRITIS AND GLAUCOMA ASSOCIATED WITH MUMPS

Iritis as a manifestation of mumps is of considerable rarity, only about 20 cases having been described since 1881. In only one previous case has an association with increased intraocular pressure been noted. An iritis of the serous type, without residual damage, is the form usually found in association with mumps. This subsides rapidly on use of heat and atropine. It is noteworthy that the iritis in the case to be reported improved rapidly on administration of pilocarpine, indicating that the iritis is probably self-limited and subsides regardless of treatment.

REPORT OF CASE

A 26-year-old white medical officer was admitted to the United States Naval Hospital, Mare Island, on Feb. 8, 1951, with a history of gradual onset of swelling of the right parotid over 18 hours. There was no history of exposure to mumps.

On admission there was a marked swelling over the right parotid gland with edema of the opening of the duct of this side. The next day bilateral involvement of the submaxillary glands appeared. On Feb. 12 the patient noted that the right eye was slightly red and uncomfortable, with some photophobia, but he assumed it was due to irritation from the parotid region. The following day a right-sided orchitis began, with tenderness and swelling of the testis on this side and elevation of temperature to 105 F. The next day the eye was still uncomfortable, and some blurring of vision was noted. Examination was done at this time in the isolation ward. There was moderate ciliary injection of the right eye, and the cornea was slightly steamy. Tension was 42 mm. Hg in the right eye and 22 mm. in the left eye. Pilocarpine, 0.5%, was ordered to be instilled q. i. d. in the right eye.

Two days later the orchitis had subsided enough that the patient could be sent to the eye clinic. The eye was then comfortable, and the vision had cleared considerably. Examination at this time revealed vision of 20/30 in the right eye and 20/15 in the left eye. There was minimal ciliary injection, and the cornea was clear. The slit lamp showed a trace of flare, no cells, but many fine punctate keratic precipitates on the posterior corneal surface. Ophthalmoscopic examination was negative. Tension at this time was 24 mm. Hg in the right eye and 21 mm. Hg in the left eye. Pilocarpine was discontinued.

The flare rapidly disappeared in the next three days. The patient was discharged on Feb. 28, with a vision of 20/15 in each eye. The tension was 22 mm. Hg in each eye. The injection was gone, and there was no flare or cells. The keratic precipitates had largely disappeared. The fields showed no constriction of the periphery with the perimeter and no enlargement of the blind spot or other scotoma with a 1/1000 white target on the tangent screen. The parotid and testicular swelling was gone, and only a slight testicular tenderness remained.

When last seen, in September, 1953, the patient had had no return of the iritis or other ocular symptoms.

RALPH S. RIFFENBURGH, M.D.
595 E. Colorado St.
Pasadena 1, Calif.

From the Department of Ophthalmology and the Oscar Johnson Institute of the Washington University Medical School.

Annual Reviews

DISEASES OF THE RETINA AND OPTIC NERVE

HENRY P. WAGENER, M.D.
ROCHESTER, MINN.

RETROLENTAL FIBROPLASIA

THE LITERATURE on retrolental fibroplasia continues to be rather voluminous. But, actually, little progress seems to have been made toward clarifying the criteria for the diagnosis, the etiology, the methods of prevention, or the treatment of this disease. As Doggart aptly puts it, only one factor has been proved in its etiology, and that is that its incidence is inversely proportional to the birth weight. Doggart [1] estimated that retrolental fibroplasia will occur in 1 of 7 premature babies with a birth weight of less than 3 lb. (1,400 gm.), in 1 of 16 with a birth weight of less than 4½ lb. (2,000 gm.) and in practically none with a birth weight of more than 5 lb. (2,300 gm.). This incidence would seem to be considerably lower than that suggested by Maumenee [2] in his 1953 review (50 to 60% of infants weighing less than 3 lb., or 1,400 gm., at birth) and emphasizes the need for clarification of the criteria for diagnosis.

Classification.—Maumenee [2] emphasizes the desirability of adoption of a "standard nomenclature for the classification and description of the disease." Such a classification was submitted by a subcommittee consisting of Drs. Reese, King, and Owens [3] and was adopted by a joint committee for the study of retrolental fibroplasia appointed by the National Society for the Prevention of Blindness. This classification should be studied in the original, as it is rather detailed and is accompanied by illustrative drawings. The earliest stage is said to be "dilatation and tortuosity of retinal vessels." However, Guy [4] thinks that this stage might be preceded by haziness of the vitreous and myopia produced by a change in the refractive index of the media. In the opinion of Szewczyk,[5] the first manifestation of the disease is edema in the periphery of the retina, the initial response to hypoxia. It should be noted that Doggart [1] considers a faint haze in the vitreous, and also a gray, slightly edematous periphery, to be normal in the eyes of premature infants. Szewczyk [5] calls attention to the fact that in the newborn streaky hemorrhages near the posterior pole of the retina may be due to birth trauma, but that blotchy hemorrhages in the midperiphery or periphery are almost always due to hypoxia. He mentions the very dilated and tortuous retinal vessels and moderate to marked edema of the peripheral retina, with hemorrhages over and at the base of the edematous retina, which are not uncommon in newborn, premature, and full-term babies. These changes, he says, are due to relative hypoxia occurring in utero or during delivery; they regress when the oxygen saturation of the blood rises at birth. A similar or identical picture may develop in premature babies after birth and is also "hypoxic retinopathy." Szewczyk [5] proposes that the term "retrolental fibroplasia" be reserved for the termi-

From the Section of Ophthalmology, Mayo Clinic and Mayo Foundation.
The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

nal phase of "hypoxic retinopathy," characterized by a total or partial retrolental mass with a normal anterior segment of the eye. Then the terminal phase of "hypoxic retinopathy," without detachment of the retina or peripheral masses, could be called "retinal fibroplasia," and the combination of a total retrolental fibrotic mass with microphthalmos, "ocular fibroplasia." There may be some merit in these terms or distinctions.

Incidence.—It has been noted that the incidence of retrolental fibroplasia varies in different localities. Guy, Dancis, and Lanman [6] examined 266 premature infants during the first two weeks of life and periodically thereafter until the diagnosis of retrolental fibroplasia could be made or excluded. They found that if the eyes were normal at the end of three months the disease would not develop. Of the babies, 142 weighed more than 2,000 gm. at birth. In none of these did retrolental fibroplasia develop. One hundred twenty-four of the babies weighed less than 2,000 gm. at birth. Of these, 77 were classified as "abnormal"; that is, vitreous haze, myopia, or dilatation and tortuosity of retinal vessels was found on examination. Of these "abnormal" infants, retrolental fibroplasia developed in 12; the authors made this diagnosis only if retinal detachment or cicatrix was present. Thus, under this interpretation, although 28.9% of the entire group, or 62.1% of the babies with a birth weight of less than 2,000 gm., were "abnormal," in only 4.5% of the entire group, or in 9.7% of the babies with a birth weight of less than 2,000 gm., did retrolental fibroplasia develop. The condition of 65 of the 77 "abnormal" babies regressed to normal. In only one baby who was considered normal at the first examination did retrolental fibroplasia develop later. The authors think that the "abnormalities" may represent simply immature eyes which are susceptible to the development of retrolental fibroplasia. Bedrossian [7] found 44 cases (34.6%) among 127 premature infants with birth weights of less than 4 lb. (1,800 gm.) but noted that a retrolental membrane does not develop in most cases. Benton [8] found only 19% of 84 similar infants affected.

It has been thought that the incidence of retrolental fibroplasia was lower in the southern states. That this is not necessarily true is shown by the studies of Ghent and Roberts in North Carolina, and of Stokes and Buckhaults in Georgia. Ghent and Roberts [9] examined 101 premature infants in one year; 60 of these weighed less than 3½ lb. (1,600 gm.). They found active retrolental fibroplasia in 6 (10%) of the latter, or in 6% of the entire group. Stokes and Buckhaults [10] found 49 cases of retrolental fibroplasia among 254 premature babies examined (19.3%). The weight of 48 infants was less than 1,500 gm.; 29 of these were affected (60.4%). The weight of 206 was more than 1,500 gm.; 20 of these were affected (9.7%). No baby with a birth weight of more than 2,175 gm. was affected. Of babies with a birth weight of less than 1,500 gm., five became blind or nearly so (10.4%). Only two babies with a birth weight of more than 1,500 gm. became blind (0.97%).

Begg and Wilson [11] report what is believed to be the first case of retrolental fibroplasia seen in New Zealand. The infant's birth weight was 2 lb. 1 oz. (936 gm.). The cicatricial stage was first observed at the age of 7½ months. Hoffmann-Egg, Tosello, and Verrey [12] state that they did not find any case of retrolental fibroplasia among 60 underweight premature babies and that they did not find any case in the course of histologic examination of 70 globes removed because of glioma, pseudoglioma, malformation, or detachment of the retina. Brændstrup and Flensborg [13]

state that retrolental fibroplasia was unknown in Denmark before 1949. However, during the past two years systematic examination of premature infants in a Copenhagen children's hospital revealed 24 cases, and 7 cases have been reported from *rigshospitalet's* eye department. Of these 31 infants, 8 are permanently blind and 4 have impaired vision. In 19 infants the changes were transitory. Lelong and others [14] examined 566 premature infants weighing less than 2,000 gm. and found 95 cases of retinal disease (16.7%). In 32 (5.65%) of these complete fibroplasia with blindness developed. In 9 (1.6%) partial detachment of the retina developed but the infants had some vision. In 54, or 56.8%, of the eyes originally involved, the condition underwent complete regression without any sequelae. Schlesinger and McCaffrey [15] sent questionnaires to the mothers of 3,377 infants whose birth weights were less than 2,000 gm. and who had survived to the age of 4 months. A total of 50 cases in which there were gross visual defects was reported (1.48%). This low incidence of ultimate visual impairment must indicate that the processes included under the term "retrolental fibroplasia" are, to some extent at least, self-limited.

Etiology and Treatment.—Although some authors, among them Guy [4] and Blodi,[16] do not agree, many observers seem inclined now to accept Szewczyk's interpretation of the relationship of relative anoxia, or hypoxia, to the development of retrolental fibroplasia and to consider proper administration of oxygen as the key to successful prevention and treatment of the disease. Szewczyk [5] has presented extensive evidence in support of his concept of the disease. He thinks that oxygen therapy should be started early and continued until all signs are gone or until maximal improvement has been obtained. The status of the retinal vessels may be used as an index to maximal regression. When the vessels have returned to normal size, it may be assumed that further improvement will not take place and that the process of weaning from oxygen may be started. He advocates the use of 60% oxygen. Bedrossian,[7] LaMotte,* Benton,[8] Hoffmann-Egg and associates,[12] Brændstrup and Flensborg,[13] and Begg and Wilson [11] all seem to favor the concept that retrolental fibroplasia develops as the result of relative anoxia of the retina, precipitated oftenest by too rapid transfer of the baby from a high oxygen to a normal atmosphere.

Huggert [17] reports his observations on 130 premature infants. He noted that the retinal vessels were often very narrow during administration of oxygen. He noted, further, that vascular dilatation and peripheral edema occurred in most cases when administration of oxygen was stopped, but that it developed in some while oxygen was still being administered. He describes one case in which the patient was successfully treated by the Szewczyk method. He calls attention to the fact that retrolental fibroplasia began to increase in incidence in the United States in 1941 and in Sweden in 1944 and 1945. Incubators with special means for administration of oxygen began to be generally used in the United States about 1940 and in Sweden in 1944.

Ashton, Ward, and Serpell [18] carried out a series of experiments to study the effects of high, moderate, and low concentrations of oxygen on growing retinal vessels. They noted that the degree of retinal vascularization in the full-term kitten, at birth and in the ensuing three weeks, is comparable to that in the premature baby. When kittens were kept in an atmosphere containing 75 to 80% oxygen for about four days, it was found that developing retinal vessels were obliterated in part and

* LaMotte, W. O., Jr., in discussion on Bedrossian.[7]

that some collapsed vessels contained trapped, coagulated blood. After transfer to air for three days, such vessels as remained patent appeared to reopen and form a grossly abnormal cobweb-like network of capillaries, with peripheral thrombi and hemorrhages. The authors thought that this process represented a specific effect on growing vessels or a fundamental interference with the process of vascularization. The hyaloid artery and other vessels in the body were not affected. The extent of vascular obliteration induced by oxygen was found to be directly proportional to the degree of immaturity of the retinal vascularization, to the duration of exposure to oxygen, and to the concentration of oxygen. The reestablished blood supply seemed to be inadequate for the retina when the animal was forced to breathe air, and vessel growth was found to recommence from the disc. New vessels were found growing into the vitreous after 18 days, and retinal detachment was observed after 30 days. The basic injury in retrolental fibroplasia would seem, then, to be vascular obliteration by the high oxygen concentrations, but vascular proliferation will not occur until the infant is placed in ordinary atmospheric conditions.†

THE RETINA IN SYSTEMIC DISEASES

Retinopathy in Diabetes.—The nature of the vascular lesions in the retina of the diabetic and their relationship to intercapillary glomerulosclerosis continue to be of interest. Goodman [20] reviews the present status of knowledge of these "specific vascular lesions of diabetes mellitus" and endorses the view that "diabetes injures the capillaries . . . and possibly the smaller arterioles of the retina and glomerulus in some as yet unexplained manner." In his opinion, "because the large arteries are generally spared in the young diabetic patient, retinopathy and glomerulosclerosis may be studied in their pure form in this group," and "characteristic lesions develop in the small blood vessels of the retina and the glomerulus and these are totally unrelated to atherosclerosis and other forms of arteriosclerosis." In his review of Lundbaek and Jensen's "Long-Term Diabetes," Mann [21] calls attention to the statement that retinopathy was present in 92% of patients with Kimmelstiel-Wilson disease and in 76% of those without this renal lesion. In view of this high percentage of retinopathy in patients with Kimmelstiel-Wilson disease, Ricketts and others [22] were surprised at its absence in a dog with spontaneous diabetes mellitus. Cohen [23] reports a case of Kimmelstiel-Wilson disease in a patient with diabetes of 13 years' duration and noted the presence of a retinopathy which he considers to be of mixed diabetic, hypertensive, and arteriosclerotic type. Murphy [24] calls attention to the fact that the presence of cotton-wool patches in the retina of a diabetic does not always mean

† Since this review was completed, it has come to my attention that Patz and his associates [19] conducted studies similar to those of Ashton and his associates and came to somewhat different conclusions. They exposed newborn rats, mice, kittens, and puppies to oxygen concentrations of 70 to 80% for varying periods up to 21 days and then studied the eyes histologically. They conclude that high oxygen concentration alone may cause the changes of retrolental fibroplasia through its constricting effect on the retinal vessels and the resultant anoxia of the retina distal to the constriction, as well as through its inhibiting effect on the normal extension of the vasculature to the peripheral retina. They think that rapid withdrawal from prolonged oxygen therapy may accentuate the injurious effect of high oxygen concentrations but that this is not the requisite or primary factor in production of retinal anoxia and the compensating abnormal vascular proliferation.

complicating hypertensive disease, as they may appear in the presence of carbuncles, infected ulcers, gangrene, or urinary tract infections and may disappear when these sources of toxemia are removed.

In his comparative study of the retinas obtained at necropsy from 21 diabetics and 21 nondiabetics, Hartford [25] confirmed the impression that microaneurysms in the retina are not pathognomonic of diabetes but occur predominantly in long-standing cases of this disease. Microaneurysms were present in 19 of the 21 diabetics and in only 6 of the 21 nondiabetics. In all but one of the nondiabetics the aneurysms were scanty and isolated.

In a further study of the capillary system in the retinas of diabetics, Ashton [26] found, in addition to the involvement of the venous side, hyaline constriction of the terminal and precapillary arterioles and partial atrophy of the capillary bed on the arterial side. He is of the opinion that this was probably a late stage in the development of the retinal disease, that it was not an indication of superadded hypertensive disease but is a characteristic late development of the diabetic process itself. It seemed possible to him that this process might not be an actual degeneration of the vessel wall but, rather, might be a deposit from the blood as a further manifestation of disturbed mucopolysaccharide metabolism. He calls attention to two types of new vessel formation—retinitis proliferans after hemorrhage into the vitreous, and rete mirabile in ischemic areas of the retina.

Treatment of Retinopathy in Diabetes Mellitus.—Poulsen [27] reports the complete regression of retinopathy in a woman, 30 years old, who had had diabetes for 21 years. The regression occurred after the development of severe hypopituitarism of the Simmonds or Sheehan type. Poulsen stated [27]:

> It can be concluded that retinopathy with numerous hemorrhages and waxy exudates can disappear and may be curable, and that the lesion is most likely a consequence of metabolic hormonal disorder in diabetes.

As it is probable that the most important factor in the causation of the retinopathy is "the unrestrained action of the pituitary or cortical adrenal hormones," it might be advantageous to consider "some means of reducing the function of the pituitary gland or adrenal cortex in young patients with severe retinopathy."

Sparks [28] noted the regression of retinopathy in a woman, aged 27, with diabetes of 17 years' duration when she was kept on a high-protein diet. He states that a high-protein diet delays the process if started in the early stage of retinopathy but has little or no effect in advanced retinopathy.

Testosterone is presumed to dampen or inhibit the pituitary and adrenal functions and to improve protein metabolism. Heinsius [29] regulated the carbohydrate metabolism of his patients and gave calcium, rutin, vitamin K, and testosterone twice a week. He states that the retinopathy did not progress in 80% of the patients so treated. Some years ago, Kepler and I treated a number of patients with severe retinopathy with high-protein diets and testosterone. No more than transient improvement was observed in any of the cases. In a carefully controlled study, Bedrossian and his co-workers [30] came to this conclusion:

> Hormone therapy with testosterone propionate or testosterone propionate and estradiol in weekly intramuscular injections, given for five months under the conditions of this study, was not demonstrably more effective in the control of diabetic retinopathy than were weekly injections of saline.

For the control of retinitis proliferans, with formation of new vessels, Trueman, Beardwood, and Smith [31] used x-ray therapy in doses of 2,400 r. They treated 52 eyes and obtained varying degrees of improvement in 29 (56%), but the improvement was only slight in 12 (23%). The retinopathy was unchanged in 16 eyes (31%) and became worse in 7 (13%).

Evidence is accumulating that rigid control of the diabetes is the best means available at present for prevention of the development of retinopathy, or at least of its progression to serious proportions. As a result of his observations in more than 100 juvenile diabetics, Krause [32] states that a patient whose disease is well controlled might have moderately severe diabetes, from childhood for 20 to 30 years, without any signs of damage to the retina; a relative few will have a few microaneurysms and small punctate exudates. Root ‡ states that of 188 patients between the ages of 25 and 38 who had had diabetes for 20 years, 28 had achieved good control. None of these had retinopathy or nephropathy. In the poorly controlled group, 25% had nephropathy and 65 to 70% had retinopathy. The reports of Styron [33] and of Sherrill [34] are not so optimistic except with respect to impairment of vision. Styron studied 519 cases. He states that no patient with diabetes for 20 years and poor control was free of retinopathy; no patient with good control had advanced retinopathy or Kimmelstiel-Wilson disease. Sherrill [34] stated that, in his opinion, restriction of total calories is the essence of dietary management of diabetics. He had 14 patients thus controlled in whom diabetes had developed before the age of 17 and who had had the disease for 20 to 30 years. Of them, 12 had retinopathy (85.7%), but the retinopathy was of Grade 1 in 10 and of Grade 2 in 2. Vision was recorded as 20/20 in 9 and 20/30 in 1. In 26 similarly controlled patients, the diabetes had developed after the age of 18 and had lasted for 20 to 38 years. Retinopathy was present in 22 (84.6%); it was of Grade 1 in 16 and of Grade 2 in 6.

It is frequently asked whether retinal lesions occur in hemochromatosis. Hudson [35] studied five patients with this disease. In three he found, in the conjunctiva, fusiform and berry aneurysms and, in another, occasional fusiform aneurysms. In one patient, a few microaneurysms of berry type were present in each retina and two small hemorrhages, similar to those seen in diabetes mellitus, in the left retina.

Hypertensive Disease.—Ophthalmologists and internists still seem dissatisfied with existing classifications of the retinal lesions associated with systemic hypertension. Scheie [36] describes the ophthalmoscopic signs of atherosclerosis and arteriolosclerosis and states that in his opinion evaluation of the severity of sclerosis of the retinal arterioles is of greater value to the internist than is grading of the severity of the hypertensive state. Therefore he proposes that narrowing and irregularity of the arterioles, and the associated nutritional changes in the retina, be considered together as signs of hypertension, various grades of which might be associated with varying grades of arteriolar sclerosis; he proposes, further, that no effort be made to combine these two distinct entities into specific groups. Gibson and Peckham [37] present a system of separately grading generalized narrowing, focal constrictions, and generalized sclerosis of the arterioles. They state that generalized narrowing

‡ Root, H. F., in discussion on papers by Drs. J. T. Beardwood Jr., G. W. Dana, and J. S. Friedenwald on Diabetic Retinitis, read at the meeting of the New York Academy of Medicine, Section of Ophthalmology, Nov. 7, 1952, A. M. A. Arch. Ophth. **50**:124-125 (July) 1953.

and focal constrictions are associated with types of hypertension that will pursue a rapid course; generalized arteriolar sclerosis is characteristically associated with a clinical course of insidious progression.

Page [38] discusses the treatment of hypertensive disease, which he classifies as essential or malignant, either variety of which might be encountered in an early, a moderately advanced, or an advanced stage. He describes the effects of the ganglion-blocking agent hexamethonium and of Apresoline (hydralazine), which is presumed to counteract one of the pressor mechanisms concerned in the production of elevated blood pressure. A number of authors point out the favorable effect of these drugs on hypertensive retinopathy, among them Smirk,[39] Grob and Langford,[40] Kummer and La Rosée,[41] and Sokolow and Schottstaedt.[42] These last authors, and Jeffers and co-workers,[43] discuss the effects of surgical treatment of hypertensive disease. By contrast, François, Verriest, and Mortier [44] describe the treatment of hypertensive retinopathy by hyperpyrexia induced by typhoid vaccine.

Singh and Bruce [45] state that the prognosis for recovery of vision is usually good in cases in which detachment of the retina occurs in the course of toxemia of pregnancy, for spontaneous reattachment tends to take place within a few weeks after the acute episode. In their case the detachments had flattened out by the 16th day, and 53 days post partum the vision was 20/25 in each eye. They noted the interesting fact that detachments of the retina in association with toxemia of pregnancy may or may not be accompanied by diffuse retinopathy. Diffuse retinopathy was present in their case, and there was permanent residual hypertension.

Syphilis.—Klauder and Meyer [46] discuss the Sidler-Huguenin classification of the chorioretinitis of congenital syphilis. They examined 223 patients with interstitial keratitis and found that 13.4% had chorioretinal lesions and 8%, perivasculitis. They examined also 54 patients who did not have interstitial keratitis and who made no complaint referable to the eyes; 7% had chorioretinitis, and 5%, perivasculitis. Of 17 patients without interstitial keratitis, but who complained of other ocular conditions, 15% had chorioretinitis and 9% had perivasculitis. The authors were not very successful in their attempts to classify the cases according to the Sidler-Huguenin groups. But they found that the retinitis pigmentosa type was very rare and did not occur in cases of acquired syphilis. Manschot and von Winning [47] report a hole in the macula caused by the traction of scar tissue which was the result of syphilitic periarteritis of the inferior macular artery.

Intracranial Bleeding.—Cordes [48] calls attention to the association of subhyaloid hemorrhages in the retina with bleeding, either traumatic or spontaneous, into the subarachnoid space; he reports two cases in which the subarachnoid bleeding was of the spontaneous type. Weinstein [49] discusses the theory of the "crush syndrome"; he tried to explain the occurrence of edema and hemorrhages in the retina in association with injuries to the skull and chest, and in association with "apoplexy," on the basis of a similar "distant neurovascular effect" (angiospasm with secondary dilatation of the capillaries and veins).

Loss of Vision Following Distant Hemorrhage.—Davenport and Budden [50] report a rather typical case of loss of vision following distant hemorrhage in which the hemorrhage came from a somewhat unusual source, snake bite. The loss of

vision occurred in one eye six days, and in the other eye eight days, after the bite. The final vision in the left eye was graded as bare light perception and in the right, as 6/5; but inferior altitudinal anopsia was present in the right eye.

Blood Dyscrasias.—Sun [51] reports his ophthalmoscopic observations on six patients with proved aplastic anemia. The early changes consisted of narrowing of the retinal arterioles and engorgement of the veins, with small, superficial, and rounded hemorrhages. Later, the vessels became pale; the disc margins blurred, and larger hemorrhages and patches of exudate appeared. Linquette, Vouters, and Goudemand [52] noted that in cases of acute leukemia the evolution of the retinopathy does not necessarily parallel the course of the disease. The retinal lesions may disappear before death. The hemorrhages are considered to be caused by thrombocytopenia.

Sarcoidosis.—Fine and Flocks [53] report bilateral acute neuroretinitis in a patient with generalized lymphadenopathy, which originally was thought to be tuberculous, but which later was proved to be sarcoidosis. There was no response to streptomycin and paraaminosalicylic acid; but under treatment with cortisone orally and corticotropin intravenously, vision returned practically to normal at the end of a month. MacLean § reports excellent results in five patients with neuroretinal periphlebitis treated with isoniazid. All gave negative tuberculin tests, but some had Landers vitreous nodules, supposedly specific for sarcoid.

Brucellosis.—Chavarria Iriarte [55] reports one case of retinal detachment, two cases of uveitis, and one case of bilateral optic atrophy which he ascribed to brucellosis. Puig Solanes and his co-workers [56] studied 413 patients with brucellosis. Positive blood cultures were obtained from more than half the patients. When a positive blood culture was not obtainable, diagnosis was established in all but one case by the coincident presence of high agglutinin titers and positive cutaneous allergy. The authors divided the ocular involvements into "pure ophthalmopathies" and "neuro-ophthalmologic disorders." They found 12 "pure ophthalmopathies," among which they included 1 instance of punctate keratitis (not definitely nummular), 1 of tenonitis, 1 of macular retinopathy, 1 of retinal phlebitis, 6 of iridocyclitis, and 2 of uveitis. They found 47 "neuro-ophthalmologic disorders," among which they included 22 instances of papillary congestion (characterized by redness of the disc, engorged veins, and demonstrable enlargement of the physiologic blind spot), 8 of papillitis, 2 of papilledema, 5 of retrobulbar neuritis, 3 of simple atrophy, 3 of postneuritic atrophy, 3 of ocular muscle paresis, and 1 of optochiasmatic arachnoiditis, which was proved surgically. The authors believe that the involvement of the optic nerve was in the form of perineuritis secondary to inflammation of the meninges in the region of the chiasm. They state that in Mexico, where human infection is almost always due to Brucella melitensis, pure brucellar ophthalmopathies are rarely observed but involvement of the optic nerves frequently is seen. The lesions of the optic nerve frequently regress to normal but may lead at times to simple, or postneuritic, optic atrophy.

Toxoplasmosis.—Koke [57] reports, as probably caused by toxoplasmosis, a case of unilateral acute central chorioretinitis which developed in a 25-year-old woman two

§ MacLean, A. L., cited by Irvine.[54]

weeks before the birth of a child. At the age of 6 months the child was found to have small eyes, with a pseudoglioma type of mass in each vitreous and intracranial calcification consistent with toxoplasmosis. Seven years later the serum of both mother and child was positive for Toxoplasma antibodies and the intracranial calcification of the child, who was mentally defective, had increased. Wilder [58] examined 58 adult eyes with strikingly similar focal inflammatory lesions involving the retina, the choroid, and, frequently, the sclera. In 53 eyes, morphologically identical protozoa resembling Toxoplasma were found. Sabin [59] states, however, that the organisms found by Wilder [58] were not proved to be Toxoplasma and that most cases of postnatally acquired chorioretinitis are not caused by Toxoplasma. Feldman [60] states, also, that there is no definite evidence that toxoplasmosis is an important factor in retrolental fibroplasia or in acute or recurrent chorioretinitis of adults. Duke-Elder and his associates [61] suggest that some of the histologic appearances resembling Toxoplasma forms may result from cellular debris or nuclear fragmentation.

Cranial Arteritis.—Kendall [62] noted that loss of vision developed in 6 of 17 patients with temporal arteritis; 4 became blind in both eyes. Attention is drawn to this because, as Payne [63] states in his 1953 annual review of neuro-ophthalmology, "many ophthalmologists and neurologists are apparently not acquainted with this group of ocular disorders." Payne [63] lists the various retinal lesions encountered in this disease. It may be worth while to mention that the presence of an elevated erythrocyte sedimentation rate in cases in which the central artery of the retina is closed, or ischemic optic neuritis is present, is suggestive of cranial arteritis.

Occlusion of the Central Artery of the Retina.—Keeney, Kasper, and Shipman [64] report a case in which closure of the central artery occurred in the course of orbital cellulitis. They express doubt that the closure was caused by the mechanical pressure of the edema in the orbit; they incline, rather, to the opinion that it resulted from the increased intraocular tension produced by splinting of the globe or by mechanical occlusion of the vortex (venae vorticosae) or of the ciliary veins. Benton [65] reports two cases in which glaucoma followed occlusion of the central artery of the retina. The investigator was able to examine histologically one of the eyes, which was enucleated because of the glaucoma. The conclusion is reached that the glaucoma that follows occlusion of the central artery of the retina is a definite secondary glaucoma, resulting from a fibrovascular peripheral anterior synechia similar to, but less extensive than, that found in glaucoma secondary to occlusion of the central retinal vein. Gillan [66] reports two cases of unilateral loss of vision following an abdominal operation during which the blood pressure was maintained at low levels by spinal block. In one case there was definite, and in the other probable, ischemic infarction of the retina. He thinks it possible that pressure on the eye by the anesthetic face mask was the direct cause of the ischemic edema of the retina but that the sustained low blood pressure made the eye more than usually susceptible to the effects of external pressure. Under the classification of "arteritis of unknown etiology," Dienstbier [67] reports cases of occlusion of the central retinal artery in young adults whose cardiovascular systems were normal.

Occlusion of the Central Retinal Vein.—Klien [68] discusses the factors involved in occlusion of the central retinal vein and reports two rather unusual cases. In the first, the occlusion was caused by an intramural thrombus arising from degenera-

tion and detachment of the intimal lining. In the second, primary phlebosclerosis affecting the fibrous part of the venous wall caused secondary hydropic degeneration and desquamation of the intimal cells, which eventually blocked the lumen.

Klien [68] thinks that her histopathologic studies revealed a sound explanation for the failure of treatment in cases of established occlusion, except in those resulting from blood dyscrasia, sepsis, or trauma. She states, also, that anticoagulant therapy might prevent venous occlusion in the fellow eye even if it did not significantly improve the already involved eye.

Cassady [69] takes a rather pessimistic view of the prospects for return of vision after thrombosis of retinal veins. He reports 54 cases, in 12 of which single branches were occluded. Final vision was less than 20/200 in 38 (70.4%). In eight (14.8%) the eye became blind or had to be enucleated. Glaucoma developed in nine eyes (16.6% of cases) after an interval of six weeks to six years. In 46 cases (85.2%) the condition was attributed to hypertension and arteriosclerosis, either one or both, and in 2 others to hypertension and diabetes. In view of recent studies on blood volume in association with vascular lesions of the retina, it is of interest that polycythemia vera was diagnosed in one case. Final vision of 20/30 or better was recorded in only five cases (9.3%). Unfortunately, the author did not differentiate clearly in his statistics between the end-results of thrombosis of venous branches and those of thrombosis of the central vein.

Somberg [70] reports excellent results in 14 cases of partial or total venous occlusion in which he gave heparin and bishydroxycoumarin U. S. P. (Dicumarol). He thinks that the venous occlusions most suitable for anticoagulant therapy are those due to endophlebitis or to factors predisposing to thrombus formation, such as increased blood volume, slowing of blood flow, high viscosity of the blood, or pressure on the vein by a sclerosed artery. He tried anticoagulant therapy in four cases of arterial occlusion, but without effect.

Innerfield and co-workers [71] mention the good results obtained in treatment of thrombosis of the central retinal vein with trypsin. This method of treatment perhaps deserves further trial and investigation.

MACULAR LESIONS

Amsler || published further papers on early visual defects accompanying lesions at the macula, studied by means of his grid. He defines "metamorphomata" and "translucent scotomata" and states that metamorphomata are caused by edema under the rods and cones displacing these retinal elements, while translucent scotomata result from edema in the conducting layers of the retina anterior to the rods and cones. He suggests methods of treatment for these lesions.

Klien [74] subdivides macular lesions of vascular origin into those limited to the retina, those involving from the start both choroid and retina, and those limited to the choroid, at least primarily. She describes the varying ophthalmoscopic appearance of these lesions and the histopathologic features of the second and third groups.

Sorsby and Crick [75] report the familial occurrence of central areolar choroidal sclerosis. They state that the earliest ophthalmoscopic appearance of this lesion is either an exudative-edematous reaction in the central area or a pigmentary mottling

|| References 72 and 73.

of the region. The picture becomes pathognomonic when there is exposure of the choroidal vessels over an areolar area. Ultimately, there is complete obliteration of the exposed choroidal vessels and of the choriocapillaris. As a result of a histopathologic study of the condition, Ashton [76] concludes that central areolar choroidal sclerosis is not the result of arteriosclerotic changes in the choroid but is a hereditary, spontaneous atrophy affecting the submacular choroidal vessels. He found that the outer layers of the retina and the pigment epithelium were absent in the area corresponding to the avascular and atrophic zone in the choroid.

Alper and Alfano [77] observed in seven members of three generations of the same family lesions which they considered to be variants of Doyne's "honeycomb colloid choroiditis." They classified their cases as representative of a familial heredodegeneration of the tapetoretinal type, characterized primarily by drusen-like masses in each centrocecal area, and later by atrophy and pigment degeneration.

Donahue [78] reports the case of a woman, aged 52, who had serious loss of vision in each eye as the result of extensive deposits of hyaline-lipid material, with some retinal atrophy, particularly concentrated in the disc-macular regions. The concentration of cholesterol in the blood was 441 mg. per 100 cc., and, with the Gofman ultracentrifuge flotation method, the blood serum was found to contain a considerably greater than normal number of giant lipoprotein molecules (S_f 10-20 series), which presumably are found only in persons with vascular disease. This article by Donahue emphasizes the advisability of studying the blood lipids of patients with early degenerative lesions of the macula. If the lipids are found to be abnormal, a low-fat diet sometimes will be of value in preventing progressive loss of vision.

Lijó Pavia [79] reports further on his cases of "tapetoretinal degeneration" with luminescent crystalline deposits in the macular retinas. No uniform specific cause was demonstrated. Aiello and Masters [80] describe an unusual lesion, which they classify as a Fuchs spot, in the macula of a myope.

RETINAL DEGENERATIONS

Teng and Katzin [81] state that cystoid degeneration of the peripheral retina is a physiologic phenomenon. It was found in all eyes examined except those of premature infants. It may be seen at the age of 5 months. Its degree increases with age. The motility of accommodation seems to be the most important causative factor. The pathologic alterations associated with cystoid degeneration are formation of holes and cysts. Large cysts may be formed by the confluence or dilatation of cystoid spaces or by both.

François and Rabaey [82] report the finding of bilateral symmetrical cysts of the retina in a woman aged 72. One eye was removed because of the presence of an orbital tumor. The cyst was found to have been formed by the confluence of peripheral microcysts. Both walls of such a cyst must be perforated for detachment of the retina to occur, the authors state. At the meeting of the Chicago Ophthalmological Society on Oct. 6, 1952, a case of bilateral congenital cyst of the retina was reported by Jarratt,[83] and it was suggested that such cysts should be differentiated from the terminal stage of cystoid degeneration of the retina.

Franceschetti [84] reports the observation for a period of years, in a brother and sister, of chorioretinal degeneration simulating retinitis punctata albescens. Vrabec [85]

reports a case in which hyaline excrescences were found histologically in the internal limiting membrane of the retina. The eye had not been examined opthalmoscopically, but the author believes that these deposits might have given the ophthalmoscopic appearance of Gunn's or Crick's dots. There has been some question whether Gunn's dots are organic pathologic lesions.

Gordon [86] reports the unusual association of vitiligo and whitening of the eyebrows and eyelashes with night blindness and loss of vision in a woman aged 25. Three of her five sisters and one brother had retinitis pigmentosa. There was loss of central vision and irregular and incomplete ring scotomas; but the choroids were semialbinotic and there was no deposition of pigment in the retina. Gordon was uncertain whether this case should be classified as one of retinitis pigmentosa "sine pigmento."

Noell [87] studied the effect on the visual cells of sodium iodoacetate and sodium iodate administered intravenously to experimental animals. He found that the histologic effect of sodium iodoacetate appeared to simulate the degeneration of the visual cells and pigment epithelium seen in retinitis pigmentosa. He concludes:

> The metabolic property which is responsible for the selective effectiveness of iodoacetate is distributed over the retinal cell population in the same manner as that property which is affected by the genetic abnormality in cases of retinitis pigmentosa.

The significance of this observation is hard to evaluate at present.

RETINAL DETACHMENT

Leydhecker [88] gave the water test to 19 patients with detachments and was not able to produce an increase in intraocular tension. He found, however, that the field defects increased temporarily in 10 of the 15 eyes examined, probably as a result of increase in the amount of subretinal fluid.

Smith and Pierce [89] analyze the results of operations for retinal detachment performed by various surgeons on the Retina Service of the Massachusetts Eye and Ear Infirmary. The criterion for a successful result was reattachment persisting for at least six months without reference to restoration of vision. Successful results were obtained in 70% of the 525 eyes subjected to operation. The authors listed the following as unfavorable preoperative prognostic signs: detachment of the macula, fixed retinal folds with or without aphakia, total detachment, multiple tears, and failure to find holes. Using the same criterion, Kennedy and Kazdan [90] obtained successful results in 47.5% of 103 consecutive cases. Interestingly, successful reattachment occurred in 71.4% of cases without holes but in only 28.6% of cases with holes. However, these authors stated that, from the patient's standpoint, the resultant visual acuity is the most important criterion of success or failure. Of the 49 cases in which the retina was reattached, vision was improved in 32 (65.3%). Thus, improvement of vision was obtained in 31% of the eyes subjected to operation.

Safar [91] states that he does not recommend surgical measures for well-demarcated detachments of the lower retina if the retina is too atrophic to promise return of the visual field. Nor does he recommend prophylactic surgical operation for retinal holes without detachment unless idiopathic detachment of the retina of the other eye has taken place. Puga [92] reports spontaneous cure in three cases of tear of the retina without detachment. In cases of retinal tear with detachment of the retina, he advocates preliminary localization of the tear by a single transconjunctival

perforating application of diathermy, so that the exact relation between the coagulated point and the tear can be determined ophthalmoscopically. Lister [93] states his opinion that chemical coagulation by a modified Lindner-Guist technique is preferable to diathermy in cases in which the retina appears to be too atrophic to stand the relatively destructive and shrinking effect of diathermy. He thinks that it might be tried also in cases in which diathermy has failed.

Lerner [94] reports the first two cases, so far as he was aware, in which tears were observed in the detached retinas of patients with retrolental fibroplasia. In both cases the retrolental changes were regressing in one eye but did not start to regress in the eye with the retinal tear and detachment until the tear had been surgically closed.

In several recent articles, authors have discussed the indications for the scleral resection operation for retinal detachment and the techniques of full-thickness and lamellar resection. Pischel and Kronfeld [95] state that their indications for the operation are as follows: (1) shortage of the retina; (2) star folds in otherwise typical detachments, with classical breaks or tears, and (3) detachments due to traction from within, such as might be exerted by vitreous strands or massive detachment of the vitreous. They describe in detail the technique of the operation, its complications, and the causes of failure. Cures (for which they required practically complete reattachment of the retina) were obtained in 46 of 150 eyes (30.6%). The operation failed in 60% of the cases. They call special attention to their lack of success in the cases in which detachments were associated with the proliferating stage of the retinopathy of diabetes. Fresh bleeding took place into the retina and vitreous immediately after surgical operation. Schepens [96] states that he has secured reattachment of the retina in 65% of 85 eyes on which he has performed the operation of scleral buckling (lamellar resection).

Stallard [97] describes modifications of the technique of lamellar scleral resection. He states that, of 30 eyes with extensive detachments of the retina for which operation was performed by this method, the retina was completely reattached in 47%. Thirty per cent of the operations were regarded as failures. Shapland [98] states that only about 25% of detachments for which full-thickness scleral resection is performed are cured. He did not bring about cure in any of his six cases. He considers cure to have been effected, however, in 38% of 50 cases in which he employed the lamellar resection technique. As indications for the operation, he lists the following: senile detachments with atrophic retina and multiple tears; myopic detachments, especially with multiple tears; old detachments; detachments without holes, in aphakic eyes; retraction of the vitreous; failure of diathermy; traumatic detachments, and detachments which do not tend to flatten out with rest and padding of the eye.

In an editorial commenting on scleral resection, McDonald [99] states that to be most effective the operation should be a primary procedure. But it should not be used indiscriminately, as the present methods of diathermy should be successful in 70% of cases. In his opinion, the operation is indicated particularly in cases in which there are fixed folds and the retina fails to settle with rest in bed. He states that it is questionable whether the immobility of the retina is caused by contraction of the posterior cortical layers of the vitreous or by shrinkage and atrophy of the retina. The purpose of the operation is sometimes said to be to provide a smaller

sphere, the inner surface of which may fit the shrunken retina. Another possibility is that the invaginated choroid makes contact with the retina and securely anchors the retina by the formation and flattening out of a chorioretinal adhesion.

TUMORS OF THE RETINA

Retinoblastoma.—Elsberg [100] reports a case of bilateral advanced tumor in which both eyes were enucleated. Mascati [101] reports the recurrence in the orbit of a retinoblastoma which, at the time of enucleation of the eye, seemed to be entirely intraocular. The recurrence was not controlled by roentgen therapy. Csapody and Kovács [102] report successful irradiation, by the Reese technique, of a retinoblastoma in the second eye. Kupfer [103] reports that in a case in which retinoblastoma developed in the remaining eye, five years after enucleation of one eye for retinoblastoma, nitrogen mustard given intravenously in combination with irradiation brought about more nearly complete regression than would be expected from irradiation alone. Henderson [104] describes a new applicator for radon seeds in the treatment of retinoblastoma.

Dunphy and Selverstone [105] found, in the study of eight enucleated eyes, that the uptake of P^{32} by three retinoblastomas was significantly higher than that of the other ocular tissues. This suggests the possibility of diagnosis of these tumors by means of a miniature in vivo counter.

Long, Black, and Danielson [106] aspirated material for examination from eight eyes immediately after enucleation. Tumor cells were found in the material from six eyes in which there was a malignant melanoma of the choroid and in two in which there was a retinoblastoma. They also took specimens for biopsy from three eyes before deciding on enucleation. The material was negative for tumor cells in one case in which the final diagnosis was retinal dysplasia and in one in which the final diagnosis was malignant melanoma of the choroid. That from the other eye, in which there was a malignant melanoma, was positive. The authors state that the only serious objection to intraocular biopsy is the possibility of spreading the tumor to the orbit or through the blood stream. This is still controversial. They think, therefore, that "aspiration biopsy should be reserved for the infrequent case in which enucleation would not be indicated unless a tumor were present and in which intensive study has not made possible a positive diagnosis." They write, furthermore: "If a positive diagnosis is obtained from biopsy, the eye should immediately be enucleated."

Teng and Katzin [107] found congenital rosettes of the retina in their histologic studies of the eyes of infants. These rosettes were of three types, occurred in the peripheral parts of the retina, and were found in 23 of the 72 eyes examined. The authors think that study of congenital rosettes might furnish clues to the histogenesis of tumors of the retina.

Angiomatosis Retinae.—Cordes and Schwartz [108] report their findings in a case of bilateral von Hippel disease, 11 years after treatment by irradiation. Vision had been preserved in the eye with the less advanced lesion, which showed scarring and atrophy. There had been no change in the enlarged vessels leading to the tumor. A small, new angioma had developed in this eye. The lens of the eye with the more advanced lesion was opaque.

The presence of angiomatosis of the retina in two patients with pheochromocytoma is reported by Glushien, Mansuy, and Littman.[109] The authors state that it has

been known that at least 10% of pheochromocytomas are associated with neurofibromatosis, and they predict that an association with tuberous sclerosis and with the Sturge-Weber syndrome (encephalotrigeminal angiomatosis) would be reported sooner or later. Payne [63] calls attention to this article in his review of neuro-ophthalmology.

PHYSIOLOGY OF THE RETINA

The Electroretinogram.—Burian [110] states that electroretinography may contribute to the understanding of disease processes in the eye, that it may help in establishing the prognosis, and that it may aid in evaluation of the function of the optic pathways, but that it is not primarily a diagnostic tool. For this reason, and because Bounds [111] published an extensive review of the subject in 1953, it would seem sufficient here to call attention to the studies of Jacobson and O'Brien [112] in pigmentary degeneration of the retina, those of Henkes [113] on the differential diagnosis of total and partial occlusion of the central retinal vein, and those of Monnier and von Berger [114] on the retinocortical time.

Oxygen and Anoxia.—Bietti [115] discusses the prognostic value, in the presence of some lesions of the retina and optic nerve, of having the patient breathe pure oxygen. He also discusses the diagnostic value of induced anoxia. Sieker and Hickam [116] note that when the patient is passed from air to tank oxygen, the retinal arterioles of normal persons constrict 11.5% and those of hypertensive persons 3.2%. They studied four patients before and after four months of rice diet. The blood pressure was lower, but there was no change in vascular reactivity. They think this indicated that the loss of vascular reactivity in hypertensive persons is not due simply to a high internal distending pressure; it usually, but not always, is associated with visible arteriolosclerosis. They found that breathing 5% carbon dioxide has very little effect on the larger retinal vessels. Hickam, Schieve, and Wilson [117] found that there is a positive correlation between retinal arterial reactivity and cerebral blood flow and that there is a significant correlation between retinal arterial reactivity to oxygen and the response of cerebral blood flow to carbon dioxide. Markedly reduced retinal arterial reactivity suggests, but does not guarantee, subnormal cerebral vascular reactivity. Average or above normal retinal reactivity is likely to be associated with normal cerebral vascular reactivity.

Glucose Utilization.—In studies by Kornblueth, Yardeni-Yaron, and Wertheimer,[118] the glucose utilization of the retina was shown to be independent of the various hormones and hormonal deficiency states tested. This was thought to indicate that the retina is a unique tissue from the standpoint of glucose metabolism, for the utilization of glucose by all other tissues, including the brain, can be altered by one or more of these hormones or deficiency states.

THE OPTIC NERVE

As most of the lesions of the optic nerve ordinarily encountered belong in the field of neuro-ophthalmology, only a few congenital defects and local lesions of the optic disc will be mentioned here.

Congenital Defects.—Smith [119] and Anderson [120] call attention to the field defects associated with congenital holes or pits in the optic disc. Bedell [121] describes these pits in his discussion of congenital anomalies of the disc; his description should

be read in the original. Bisland [122] reports six cases in which congenital preretinal or prepapillary loops were present and states that knowledge of the mechanism of their development is only speculative. Proksch [123] observed that, as a rule, children have only a small excavation or vessel funnel in the disc and that the larger excavations are found in older persons. She reasons, therefore, that the physiologic excavation increases normally with age, probably because of atrophy of connective and glial tissue. She thinks that this might help to account for the far-advanced cupping seen in the chronic glaucoma of elderly patients with only slightly elevated tensions.

Tumors of the Papilla.—Patterson [124] reports a melanoma of the optic disc which was seen ophthalmoscopically as a large, black, feathery mass obscuring the optic disc, associated with solid detachment of the retina. Nakayama [125] observed, in a woman aged 19, a swelling of the disc accompanied by reduction of vision to the ability to see hand movements. His original diagnosis was optic neuritis. However, 16 weeks later a brown-black tumor was visible on the disc. Histopathologic examination of the eye after enucleation revealed a melanosarcoma primary in the optic nerve. Trueman and Rubin [126] describe what they believe to be the third tumor of the nerve head to be described as being found in examination of a patient with generalized neurofibromatosis. Dolcet [127] reports a case of tubercle of the optic papilla and states that, in his opinion, in many cases papillary edema is caused by a tubercle of the papilla behind the lamina cribrosa or adjacent to it. For treatment of tuberculous meningitis in children, rather than streptomycin, he favors the hydrazine of nicotinic acid (isoniazid). He found that with use of this drug tubercles in the choroid healed, edema of the disks receded, and oculomotor paresis disappeared.

CORTISONE AND CORTICOTROPIN IN DISEASES OF THE RETINA AND OPTIC NERVE

Gordon, McLean, and Koteen [128] list, among conditions that respond favorably to cortisone and corticotropin, optic and retrobulbar neuritis and central serous retinopathy. They found that diabetic retinopathy, retinitis pigmentosa, and retrolental fibroplasia did not respond. Smith [129] reports rapid subsidence of edema of the disc and improvement of vision brought about by the use of intravenously administered corticotropin after the optic neuritis had failed to respond to treatment with cortisone, nicotinic acid, and chloramphenicol. It must be noted, however, that intravenous administration of corticotropin was started in the sixth week of the disease, when spontaneous improvement might be expected to begin.

Riddell [130] states that cortisone and corticotropin seemed to have an initially favorable effect on acute, but not on chronic, chorioretinal lesions. However, Wolfson and Quinn [131] report good results in the treatment of chronic "irreversible" neuroretinal disorders by prolonged administration of corticotropin.

Riddell [130] states, further, that the results obtained in the treatment of central serous retinopathy were difficult to assess and that retinal and choroidal degenerative lesions, such as retinitis pigmentosa, did not respond. He notes that the effects of these agents on retinal periphlebitis and recurrent hemorrhages into the vitreous have not been good. In this connection, it is of interest that Benedict and Hollenhorst [132] noted that in experimental animals the speed of absorption of hyphema was reduced after administration of cortisone. They think that the poor response to the use of cortisone and corticotropin in some forms of senile macular degeneration, in

the disciform type of macular degeneration, and in inflammatory types of choroidal or retinal disease with a hemorrhagic component might be explained if the hormones actually retard the rate of absorption of the extravasated blood. They think that use of cortisone is definitely contraindicated in treatment of hyphema, and probably also in treatment of other conditions associated with intraocular bleeding.

REFERENCES §

1. Doggart, J. H.: Retrolental Fibroplasia, Practitioner **170**:458-464 (May) 1953.

2. Maumenee, A. E.: Diseases of the Retina, A. M. A. Arch. Ophth. **49**:553-586 (May) 1953.

3. Reese, A. B.; King, M. J., and Owens, W. C.: A Classification of Retrolental Fibroplasia, Am. J. Ophth. **36**:1333-1335 (Oct.) 1953.

4. Guy, L. P.: Retrolental Fibroplasia: A Clinical Report, Tr. Sec. Ophth., A. M. A., pp. 74-80, 1952.

5. Szewczyk, T. S.: Retrolental Fibroplasia and Related Ocular Diseases, Am. J. Ophth. **36**:1336-1361 (Oct.) 1953.

6. Guy, L. P.; Dancis, J., and Lanman, J. T.: Retrolental Fibroplasia: Ophthalmoscopic Findings During the First Two Weeks of Life, Am. J. Ophth. **36**:85-89 (Jan.) 1953.

7. Bedrossian, R.: Retinopathy of Prematurity (Retrolental Fibroplasia) and Its Relationship to Oxygen, A. M. A. Arch. Ophth. **50**:266 (Aug.) 1953.

8. Benton, C. D.: Detection and Management of Retrolental Fibroplasia: A Plan for the Average Hospital and Staff, Guildcraft **27**:15, 1953.

9. Ghent, T. D., and Roberts, R. W.: Retrolental Fibroplasia in Piedmont, North Carolina, North Carolina M. J. **14**:159-161 (April) 1953.

10. Stokes, J. J., and Buckhaults, W. W.: The Incidence of Retrolental Fibroplasia in Premature Infants, Georgia M. A. J. **42**:381-382 (Aug.) 1953.

11. Begg, N. C., and Wilson, R. P.: Retrolental Fibroplasia: Report of a Case, New Zealand M. J. **52**:30-34 (Feb.) 1953.

12. Hoffmann-Egg, L.; Tosello, A., and Verrey, F.: Beitrag zur retrolentalen Fibroplasie, Ophthalmologica **125**:389-393 (April-May) 1953.

13. Brændstrup, P., and Flensborg, E. W.: Retrolental Fibroplasi, Ugesk. læger **115**:317-324 (Feb.) 1953.

14. Lelong, M.; Rossier, A.; Fontaine, M.; Lemasson, C.; Michelin, J., and Audibert: Sur la rétinopathie des prématurés (fibroplasie rétrolentale), Arch. franç. pédiat. **9**:897-914, 1953.

15. Schlesinger, E. R., and McCaffrey, I.: Incidence of Gross Visual Defects Due to Retrolental Fibroplasia, Pediatrics **11**:238-245 (March) 1953.

16. Blodi, F. C.: Retrolental Fibroplasia, Am. J. Nursing **53**:718-720 (June) 1953.

17. Huggert, A.: Supply of Oxygen to Prematures and the Appearance of Retrolental Fibroplasia, Acta pediat. **42**:147-156 (March) 1953.

18. Ashton, N.; Ward, B., and Serpell, G.: Role of Oxygen in the Genesis of Retrolental Fibroplasia: A Preliminary Report, Brit. J. Ophth. **37**:513-520 (Sept.) 1953.

19. Patz, A.; Eastham, A.; Higginbotham, D. H., and Kleh, T.: Oxygen Studies in Retrolental Fibroplasia: II. Production of the Microscopic Changes of Retrolental Fibroplasia in Experimental Animals, Am. J. Ophth. **36**:1511-1522 (Nov.) 1953.

20. Goodman, J. I.: Specific Vascular Lesions of Diabetes Mellitus: II. Retinopathy and Intercapillary Glomerulosclerosis, Am. J. Ophth. **36**:957-966 (July) 1953.

§ The articles corresponding with the following reference numbers were read by me personally not in the original but only in abstract form: 12, 13, 14, 15, 16, 17, 22, 29, 39, 40, 41, 42, 44, 51, 52, 55, 61, 67, 73, 84, 85, 88, 91, 92, 102, 109, 114, 120, 123, 125, and 127.

21. Mann, W. A.: Book Review: Lundbaek, K., and Jensen, V. A.: Long-Term Diabetes, Am. J. Ophth. **36**:1764 (Dec.) 1953.

22. Ricketts, H. T.; Petersen, E. S.; Steiner, P. E., and Tupikova, N.: Spontaneous Diabetes Mellitus in the Dog: An Account of Eight Cases, Diabetes **2**:288-293 (July-Aug.) 1953.

23. Cohen, M.: Kimmelstiel-Wilson Syndrome: Review of the Literature and a Report of a Case with the Ophthalmoscopic Findings, Am. J. Ophth. **36**:243-247 (Feb.) 1953.

24. Murphy, E. S.: Diabetic Retinopathy, Rocky Mountain M. J. **50**:562-564 (July) 1953.

25. Hartford, J. J.: Retinal Vascular Changes in Diabetes Mellitus, Am. J. Ophth. **36**:324-330 (March) 1953.

26. Ashton, N.: Arteriolar Involvement in Diabetic Retinopathy, Brit. J. Ophth. **37**:282-292 (May) 1953.

27. Poulsen, J. E.: The Houssay Phenomenon in Man: Recovery from Retinopathy in a Case of Diabetes with Simmonds' Disease, Diabetes **2**:7-12 (Jan.-Feb.) 1953.

28. Sparks, M. I.: Treatment of Late Complications of Diabetes, Am. Pract. & Digest Treat. **4**:9-11 (Jan.) 1953.

29. Heinsius, Ernst: Ist die Behandlung der Retinitis diabetica durch den Augenarzt möglich?, Wein. klin. Wchnschr. **65**:57-58 (Jan.) 1953.

30. Bedrossian, R. H.; Pocock, D. S.; Harvey, W. F., Jr., and Sindoni, A. S.: Diabetic Retinopathy Treated with Testosterone, A. M. A. Arch. Ophth. **50**:277-281 (Sept.) 1953.

31. Trueman, R. H.; Beardwood, J. T., Jr., and Smith, J. J.: X-Ray Therapy in Retinopathy, Diabetes **2**:13-22 (Jan.-Feb.) 1953.

32. Krause, A. C.: Ophthalmoscopic Changes in Children with Diabetes Mellitus, Am. J. Ophth. **36**:849-851 (June) 1953.

33. Styron, C. W.: Prevention and Treatment of Degenerative Complications of Diabetes Mellitus, South. M. J. **46**:1057-1061 (Nov.) 1953.

34. Sherrill, J. W.: Diabetes Mellitus and Diabetic Retinitis: Factors Influencing Regulation, California Med. **78**:197-203 (March) 1953.

35. Hudson, J. R.: Ocular Findings in Haemochromatosis, Brit. J. Ophth. **37**:242-246 (April) 1953.

36. Scheie, H. G.: Evaluation of Ophthalmoscopic Changes of Hypertension and Arteriolar Sclerosis, A. M. A. Arch. Ophth. **49**:117-138 (Feb.) 1953.

37. Gibson, G. G., and Peckham, R. H.: Retinal Arteriolar Signs of Hypertension, Postgrad. Med. **13**:239-248 (March) 1953.

38. Page, I. H.: Management of Moderately Severe Arterial Hypertension, Circulation **7**:116-126 (Jan.) 1953.

39. Smirk, F. H.: Action of a New Methonium Compound in Arterial Hypertension; Pentamethylene 1:5-bis-N-(N-Methyl-Pyrrolidinium) Bitartrate (M. & B. 2050A), Lancet **1**:457-464 (March 7) 1953.

40. Grob, D., and Langford, H. G.: Further Observations on the Effects of Autonomic Blocking Agents in Patients with Hypertension: I. General Systemic Effects of Hexamethonium, Pentamethonium, and Hydrazinophthalazine, Circulation **8**:205-223 (Aug.) 1953.

41. Kummer, P., and La Rosée, R. V.: Über die Hochdrucktherapie mit Hydrazinophthalazinen, München. med. Wchnschr. **95**:729-732 (June) 1953.

42. Sokolow, M., and Schottstaedt, M. F.: Management of Malignant Hypertension, Ann. Int. Med. **38**:647-666 (April) 1953.

43. Jeffers, W. A.; Zintel, H. A.; Hafkenschiel, J. H.; Hills, A. G.; Sellers, A. M., and Wolferth, C. C.: Evaluation of Adrenal Resection and Sympathectomy in 99 Persons with Hypertension, J. A. M. A. **153**:1502-1505 (Dec. 26) 1953.

44. François, J.; Verriest, G., and Mortier, G.: La pyrétothérapie par le vaccin typhique dans le traitement des rétinopathies hypertensives, Ann. ocul. **186**:62-79 (Jan.) 1953.

45. Singh, B. P., and Bruce, R. A.: Pregnancy Toxemia with Bilateral Retinal Separation, Am. J. Obst. & Gynec. **65**:186-188 (Jan.) 1953.

46. Klauder, J. V., and Meyer, G. P.: Chorioretinitis of Congenital Syphilis, A. M. A. Arch. Ophth. **49**:139-157 (Feb.) 1953.

47. Manschot, W. A., and von Winning, C. H. O. M.: Hole in the Macula Due to Syphilis, Am. J. Ophth. **36**:261-262 (Feb.) 1953.

48. Cordes, F. C.: Subhyaloid Hemorrhage Following Subarachnoid Hemorrhage, Am. J. Ophth. **36**:1192-1198 (Sept.) 1953.

49. Weinstein, P.: The Crush Syndrome in Ophthalmology, Am. J. Ophth. **36**:660-662 (May) 1953.

50. Davenport, R. C., and Budden, F. H.: Loss of Sight Following Snake Bite, Brit. J. Ophth. **37**:119-121 (Feb.) 1953.

51. Sun, S. F.: Fundus Changes in Aplastic Anemia, Chinese M. J. **71**:45-53 (Jan.-Feb.) 1953.

52. Linquette, Vouters, and Goudemand: La rétinopathie de la leucose aiguë est-elle spécifique? (A propos de 15 observations), Arch. opht. **12**:699-710, 1952.

53. Fine, M., and Flocks, M.: Bilateral Acute Neuroretinitis with Sarcoidosis Treated with Corticotropin and Cortisone, A. M. A. Arch. Ophth. **50**:358-362 (Sept.) 1953.

54. Irvine, S. R.: The Wilmer Meeting, Editorial, Am. J. Ophth. **36**:994-996 (July) 1953.

55. Chavarria Iriarte, F. A.: Manifestaciones oculares de la brucelosis, Arch. Soc. oftal. hispano-am. **13**:179-198 (Feb.) 1953.

56. Puig Solanes, M.; Heatley, Juan; Arenas, Francisco, and Ibarra, G. G.: Ocular Complications in Brucellosis, Am. J. Ophth. **36**:675-689 (May) 1953.

57. Koke, M. P.: Probable Toxoplasmic Chorioretinitis, Am. J. Ophth. **36**:845-846 (June) 1953.

58. Wilder, H. C.: Toxoplasma-like Protozoa in Chorioretinitis in Adults, Am. J. Trop. Med. **2**:417-419 (May) 1953.

59. Sabin, A. B.: Toxoplasmosis: Current Status and Unsolved Problems: Introductory Remarks, Am. J. Trop. Med. **2**:360-364 (May) 1953.

60. Feldman, H. A.: Clinical Manifestations and Laboratory Diagnosis of Toxoplasmosis, Am. J. Trop. Med. **2**:420-428 (May) 1953.

61. Duke-Elder, S.; Ashton, N., and Brihaye-van Geertruyden, M.: Toxoplasmosis in the Adult, Brit. J. Ophth. **37**:321-329 (June) 1953.

62. Kendall, D.: Some Complications of Temporal Arteritis, Brit. M. J. **2**:418-420 (Aug. 22) 1953.

63. Payne, F.: Neuro-Ophthalmology, A. M. A. Arch. Ophth. **50**:644-666 (Nov.) 1953.

64. Keeney, A. H.; Kasper, K. A., and Shipman, J. S.: Central Retinal Artery Occlusion in Orbital Inflammation, Am. J. Ophth. **36**:346-349 (March) 1953.

65. Benton, C. D., Jr.: Glaucoma Following Occlusion of Central Retinal Artery, A. M. A. Arch. Ophth. **49**:280-284 (March) 1953.

66. Gillan, J. G.: Two Cases of Unilateral Blindness Following Anesthesia with Vascular Hypotension, Canad. M. A. J. **69**:294-296 (Sept.) 1953.

67. Dienstbier, E. Z.: Nový druk arteritid sítnice a zrakového nervu, Ceskoslov. oftal. **9**:15-22, 1953.

68. Klien, B. A.: Occlusion of the Central Retinal Vein: Clinical Importance of Certain Histopathologic Observations, Am. J. Ophth. **36**:316-324 (March) 1953.

69. Cassady, J. V.: Central Retinal Vein Thrombosis, Am. J. Ophth. **36**:331-335 (March) 1953.

70. Somberg, J. S.: Anticoagulant Therapy in Retinal Vessel Occlusions, Permanente Found. M. Bull. **10**:327-331 (Feb.) 1953.

71. Innerfield, I.; Angrist, A., and Schwarz, A.: Parenteral Administration of Trypsin: Clinical Effect in 538 Patients, J. A. M. A. **152**:597-605 (June 13) 1953.

72. Amsler, M.: Earliest Symptoms of Diseases of the Macula, Brit. J. Ophth. **37**:521-537 (Sept.) 1953.

73. Amsler, M.: Zur Frühdiagnose und Frühbehandlung von Makulaerkrankungen, Klin. Monatsbl. Augenh. **122**:385-388, 1953.

74. Klien, B. A.: Macular Lesions of Vascular Origin: II. Functional Vascular Conditions Leading to Damage of the Macula Lutea, Am. J. Ophth. **36**:1-13 (Jan.) 1953.

75. Sorsby, A., and Crick, R. P.: Central Areolar Choroidal Sclerosis, Brit. J. Ophth. **37**: 129-139 (March) 1953.

76. Ashton, N.: Central Areolar Choroidal Sclerosis: A Histo-Pathological Study, Brit. J. Ophth. **37**:140-147 (March) 1953.

77. Alper, M. G., and Alfano, J. A.: Honeycomb Colloid Degeneration of the Retina, A. M. A. Arch. Ophth. **49**:392-399 (April) 1953.

78. Donahue, H. C.: Unusual Type of Degenerative Retinopathy, Am. J. Ophth. **36**:921-924 (July, Pt. 1) 1953.

79. Lijó Pavía, J.: Tapetoretinal Degeneration: Report of 4 Cases of a Rare Form of Luminescent Crystalline Tapetoretinal Degeneration, with a Discussion of Its Cause, Am. J. Ophth. **36**:1416-1427 (Oct.) 1953.

80. Aiello, J. S., and Masters, S.: Fuchs's Spot in the Macula: Rare Lesion Seen in Myopic Patients, Am. J. Ophth. **36**:1126-1128 (Aug.) 1953.

81. Teng, C. C., and Katzin, H. M.: An Anatomic Study of the Peripheral Retina: II. Peripheral Cystoid Degeneration of the Retina; Formation of Cysts and Holes, Am. J. Ophth. **36**:29-39 (Jan.) 1953.

82. François, J., and Rabaey, M.: Histopathological Examination of a Bilateral Symmetrical Cyst of the Retina, Brit. J. Ophth. **37**:601-608 (Oct.) 1953.

83. Jarratt, W. D.: Bilateral Retinal Cyst, Am. J. Ophth. **36**:1748-1749 (Dec.) 1953.

84. Franceschetti, A.: Dégénérescence choriorétinienne familiale avec angiosclérose choroïdienne, stade tardif d'une retinitis punctata albescens, constatée 54 ans auparavant, Ophthalmologica **125**:340-341 (April-May) 1953.

85. Vrabec, F.: Les verrucosités de la limitante interne de la rétine, Ophthalmologica **125**: 164-168 (March) 1953.

86. Gordon, D. M.: Retinitis Pigmentosa "Sine Pigmento" Associated with Vitiligo of the Skin, A. M. A. Arch. Ophth. **50**:372-374 (Sept.) 1953.

87. Noell, W. K.: Experimentally Induced Toxic Effects on Structure and Function of Visual Cells and Pigment Epithelium, Am. J. Ophth. **36**:103-114 (June, Pt. 2) 1953.

88. Leydhecker, W.: Die Wassertrinkprobe bei Netzhautablösung, Klin. Monatsbl. Augenh. **122**:272-276, 1953.

89. Smith, T. R., and Pierce, L. H.: Idiopathic Detachment of the Retina, A. M. A. Arch. Ophth. **49**:36-44 (Jan.) 1953.

90. Kennedy, R. J., and Kazdan, P.: End Results in Retinal Detachment Surgery, Cleveland Clin. Quart. **20**:441-444 (Oct.) 1953.

91. Safar, K.: Zur Frage der prophylaktischen Operation von Netzhautrissen und Löchern ohne Netzhautablösung, Klin. Monatsbl. Augenh. **122**:277-286, 1953.

92. Puga, R.: Localização transconjunctival das rasgaduras retinianas nevs e notas clinico-cirurgicas sobre o descolamento da retina, Arch. Soc. oftal. hispano-am. **13**:154-159 (Feb.) 1953.

93. Lister, A.: Experiences with the Lindner-Guist Operation, Brit. J. Ophth. **37**:305-311 (May) 1953.

94. Lerner, H. A.: Surgical Management of Retinal Detachment with Retinal Tears in Retrolental Fibroplasia, Arch. Ophth. **50**:64-67 (July) 1953.

95. Pischel, D. K., and Kronfeld, P. C.: The Scleral Resection Operation for Retinal Detachment, Am. J. Ophth. **36**:629-640 (May) 1953.

96. Schepens, C. L.: Prognosis and Treatment of Retinal Detachment, Am. J. Ophth. **36**:1739 (Dec.) 1953.

97. Stallard, H. B.: Technique of Lamellar Scleral Resection, Brit. J. Ophth. **37**:223-228 (April) 1953.

98. Shapland, C. D.: Scleral Resection—Lamellar or Penetrating?, Brit. J. Ophth. **37**:177-180 (March) 1953.

99. McDonald, P. R.: The Scleral Resection Operation, Editorial, Am. J. Ophth. **36**:1757-1758 (Dec.) 1953.

100. Elsberg, C. P.: Bilateral Retinoblastoma, Southwestern Med. **34**:244-246; 251 (July) 1953.

101. Mascati, N. T.: Retinoblastoma: Report of a Case, J. Internat. Coll. Surgeons **20**:196-199 (Aug.) 1953.

102. Csapody, I., and Kovács, A.: Röntgenbehandlung von Gliomaugen, Klin. Monatsbl. Augenh. **122**:43-51, 1953.

103. Kupfer, Carl: Retinoblastoma Treated with Intravenous Nitrogen Mustard, Am. J. Ophth. **36**:1721-1723 (Dec.) 1953.

104. Henderson, J. W.: Intracavitary Optic Radon Applicator, Tr. Am. Acad. Ophth. **57**: 614-615 (July-Aug.) 1953.

105. Dunphy, E. B., and Selverstone, Bertram: Uptake of Radioactive Phosphorus by Normal and Neoplastic Ocular Tissues, Am. J. Ophth. **36**:774-776 (June) 1953.

106. Long, J. C.; Black, W. C., and Danielson, R. W.: Aspiration Biopsy in Intraocular Tumors, A. M. A. Arch. Ophth. **50**:303-310 (Sept.) 1953.

107. Teng, C. C., and Katzin, H. M.: An Anatomic Study of the Peripheral Retina: III. Congenital Retinal Rosettes, Am. J. Ophth. **36**:169-185 (Feb.) 1953.

108. Cordes, F. C., and Schwartz, Ariah: Angiomatosis Retinae (von Hippel's Disease) 11 Years After Irradiation, Am. J. Ophth. **36**:1362-1367 (Oct.) 1953.

109. Glushien, A. S.; Mansuy, M. M., and Littman, D. S.: Pheochromocytoma: Its Relationship to the Neurocutaneous Syndromes, Am. J. Med. **14**:318-327 (March) 1953.

110. Burian, H. M.: Electroretinography and Its Clinical Application, A. M. A. Arch. Ophth. **49**:241-256 (March) 1953.

111. Bounds, G. W., Jr.: The Electroretinogram: A Review of the Literature, A. M. A. Arch. Ophth. **49**:63-89 (Jan.) 1953.

112. Jacobson, J., and O'Brien, J. M.: Electroretinographic Studies in Cases of Pigmentary Degeneration, A. M. A. Arch. Ophth. **49**:375-381 (April) 1953.

113. Henkes, H. E.: Electroretinography in Circulatory Disturbances of the Retina: 1. Electroretinogram in Cases of Occlusion of Central Retinal Vein or of One of Its Branches, A. M. A. Arch. Ophth. **49**:190-201 (Feb.) 1953.

114. Monnier, M., and von Berger, G. P.: Analyse des ripostes électriques du centre visuel cortical à la stimulation lumineuse chez l'homme, Ophthalmologica **126**:15-34 (July) 1953.

115. Bietti, G.: Effects of Experimentally Decreased or Increased Oxygen Supply in Some Ophthalmic Diseases: Practical Value for Diagnosis, Prognosis, and Treatment, A. M. A. Arch. Ophth. **49**:491-513 (May) 1953.

116. Sieker, H. O., and Hickam, J. B.: Normal and Impaired Retinal Vascular Reactivity, Circulation **7**:79-83 (Jan.) 1953.

117. Hickam, J. B.; Schieve, J. F., and Wilson, W. P.: The Relation Between Retinal and Cerebral Vascular Reactivity in Normal and Arteriosclerotic Subjects, Circulation **7**:84-87 (Jan.) 1953.

118. Kornblueth, W.; Yardeni-Yaron, E., and Wertheimer, E.: Glucose Utilization of the Retina: II. Influence of Various Hormones on the Glucose Utilization of the Retina, A. M. A. Arch. Ophth. **50**:500-505 (Oct.) 1953.

119. Smith, R.: Crater-like Hole in the Optic Disc, Brit. J. Ophth. **37**:122-123 (Feb.) 1953.

120. Anderson, O. C.: Grubenbildungen auf der Papille mit Gesichtsfeldausfällen, Klin. Monatsbl. Augenh. **122**:159-168, 1953.

121. Bedell, A. J.: Clinical Significance of Some Congenital Changes in the Optic Disk, Tr. Sect. Ophth., A. M. A., pp. 22-33, 1952.

122. Bisland, T.: Vascular Loops in the Vitreous, A. M. A. Arch. Ophth. **49**:514-529 (May) 1953.

123. Proksch, M.: Über die Altersveränderung der physiologischen Exkavation, Klin. Monatsbl. Augenh. **122**:168-172, 1953.

124. Paterson, M. W.: Melanoma of the Optic Disk, Brit. J. Ophth. **36**:447-452 (Aug.) 1952.

125. Nakayama, M.: Melanosarcoma of the Optic Nerve Disc: A Case Report, Acta soc. ophth. Japan. **57**:167-169, 1953.

126. Trueman, R. H., and Rubin, I. E.: Tumor of the Optic Disk Associated with Neurofibromatosis, A. M. A. Arch. Ophth. **50**:468-474 (Oct.) 1953.

127. Dolcet, L.: Tuberculo papilar y Rimifon, Arch. Soc. oftal. hispano-am. **12**:1418-1425 (Dec.) 1952.

128. Gordon, D. M.; McLean, J. M., and Koteen, H.: Present Status of Corticotropin, Cortisone, and Hydrocortisone in Ophthalmology, Tr. Sect. Ophth., A. M. A., pp. 196-216, 1952.

129. Smith, E. L.: Intravenous Use of Corticotropin in Optic Neuritis, A. M. A. Arch. Ophth. **49**:303-312 (March) 1953.

130. Riddell, W. J. B.: Cortisone and ACTH in Ophthalmology, Practitioner **170**:452-457 (May) 1953.

131. Wolfson, W. Q., and Quinn, J. R.: The "Delayed Therapocorticoid Effect," a Previously Undescribed Action of Adrenal Cortical Hormones: Its Importance for Successful Treatment of Eye Disease, Proc. Central Soc. Clin. Res. **26**:116 (Oct.) 1953.

132. Benedict, W. H., and Hollenhorst, R. W.: Influence of Cortisone on the Rate of Blood Absorption from the Eye, Am. J. Ophth. **36**:247-249 (Feb.) 1953.

Correspondence

BERYLLIUM AND DELAYED CORNEAL HEALING

To the Editor:—In the January, 1954, issue of the ARCHIVES, I read with interest an article entitled "Beryllium and Delayed Corneal Healing" by Drs. Gregory Flynn and Morgan Raiford.

In their report it was mentioned that no cases involving the cornea with beryllium were found. I wish to call your attention to an article, "Beryllium Granulomas of the Anterior Ocular Structures" (*New York J. Med.* **51**:1065 [April 15] 1951), in which I did mention involvement of the left cornea with beryllium phosphors.

I thought it would be proper to rectify this situation.

A. BENEDICT RIZZUTI, M.D.
160 Henry St., Brooklyn.

OCULAR DOMINANCE AND HANDEDNESS

To the Editor:—A full discussion of the stimulating paper by George and Dorothy Berner, entitled "Relation of Ocular Dominance, Handedness, and the Controlling Eye in Binocular Vision" (A. M. A. ARCH. OPHTH. **50**:603-608 [Nov.] 1953), requires more space than the paper itself. From their good clinical results it must be concluded that their treatment of reading difficulties is effective, but I cannot escape the impression that the basis of their reasoning is incorrect. Two points can be singled out.

In discussing their technique of examination, the authors state: "Notation of hand use should be made, including any attempted or accomplished change of handedness." Now, the determination of handedness is not possible by merely "noting the hand use." Bethe and his school, and others, have shown that it is wrong to assume that all non-left-handed people are right-handed. Among the apparently right-handed are a large number of completely and successfully converted left-handed persons, most of whom might be found by questioning, as was done by the Berners, and an even larger group of those born ambidextrous. With proper methods, it can be shown that 25% of any large group are born right-handed, 25% are born left-handed, and 50% are born without any preponderance of one hand or the other, but follow the trend of our right-handed culture and grow up as right-handed. The corresponding figures in the paper under discussion are these: right-handed, 337; left-handed, 68, and ambidextrous, 61. Hence, there must be a large number of converted but undetected left-handed and ambidextrous persons in their right-handed group. This seems to make the authors start off with an incorrect premise. If we juggle the figures a little and assume that half the left-handed were found and that the other half were undetected converted left-handed persons, we have 136 who were left-handed and an equal group, of 136, who were truly right-handed, and the rest, or 201, were right-hand-converted ambidextrous persons; add the 61 ambidextrous persons of their own statistics, and we find the authors actually dealt with 136 true right-handed, 136 true left-handed, and 262 ambidextrous persons. This new distribution is surprisingly close to the 25:50:25 ratio claimed above!

The second point is this: All methods of determining the eyedness, including the one used by the Berners (Keystone Visual Skill test), use the macular area. But there are very good reasons to assume that each macula is represented in both hemispheres. Since nobody will deny that eyedness, like handedness, is determined by

the preponderance of one hemisphere, the macula is the wrong test object. In 1934 I published a paper in which I discussed this situation and gave the results of a method devised to test the temporal half of each retina, and thus the right and left hemisphere separately. The conclusion I arrived at was that predominance of one visual field over the other (right or left half), i. e., predominance of one hemisphere, is most likely to exist, so that one must not speak of "eyedness" at all. The partial crossing of the visual fibers in the chiasm and the representation of the macula in both hemispheres can only admit of a predominance of the right or the left visual field, not of the right or the left eye.

It would be a fascinating task to apply this premise and the deliberations of the Berners to a group of people reading from right to left, as in Hebrew or Arabic. It would not be surprising to find that the situation is completely reversed in such a group. And heaven knows what we would find among the Chinese, who read from top to bottom!

JOHN J. STERN, M.D.
3 Hopper St.
Utica, N. Y.

To the Editor:—We appreciate your thoughtful discussion of our paper, published in the November, 1953, issue of the ARCHIVES. Our original paper was longer and contained discussions of the points you have made. In shortening it for publication, we had to omit many interesting, but not "central," portions of the material.

The selection of the term "hand use" was deliberate and was intended to make the point that we were not trying to determine the child's original "handedness." Most of the hand-use patterns are set by the time we see the children, and there is great resistance to any change. We have elaborated this point in the privately printed supplement, stating that when a child uses two hands, we select for constant use the one showing greater manual dexterity for fine performances, such as printing. As a rule converted left-handed children cannot or will not return to the use of the left hand. The fact that they were originally left-handed is not operative at the level of learning to read; they are now right-handed, and eye-hand coordination must conform to this pattern. The same condition applies to your suggested 50% who have no hand preference at birth and who follow cultural patterns in becoming right-handed. At the time of learning to read they are factually right-handed. Reading patterns must conform to this state.

We believe that all previous attempts to solve the problem with which we are dealing failed because they clung in one way or another to a concept of "eyedness." Some investigators attempted to locate this eyedness by determining a preferred hemisphere of the brain. (As you point out, this preferred hemisphere affects field, rather than macular, vision.) It is, of course, the maculae which are primarily concerned in reading. Those who have recognized this point had attempted to place the controlling macula as identical with the dominant (sighting) eye. Sighting is essentially a monocular act, and the sighting eye does not correlate with the controlling eye, whose macula controls acts and memory patterns initiated by binocular vision.

We have based our work on an entirely new concept. Since visual-motor coordination arises from a complicated cortical pattern, initiated in binocularly fused visual images, we looked for a pattern within binocular vision which would explain these difficulties. The entire concept of amblyopia ex anopsia supposes rivalry between the maculae in the formation of binocular vision patterns, with a positive rejection mechanism (undoubtedly psychological, rather than physiological) available to suppress an offending or unwanted image. We could, therefore, presume that training could readjust the balance of reception and establish superior reception from one macula, which had previously been affected by the rejection mechanism that, operating in a greater degree, might have caused it to be amblyopic. We aimed to place the superior macular reception on the same side as that of the hand used.

Especially in the case of converted lefthandedness, this probably places the whole development of visual-motor coordination on the side of the brain opposite the original dominant hemisphere. Duke-Elder (Text-Book of Ophthalmology, Vol. 4, St. Louis, C. V. Mosby Company, 1949) says: "We may therefore assume that since it is the determining factor, cerebral dominance has the same incidence as handedness, that fundamentally it is an innate inherited characteristic of the brain, but that an acquired dominance may be transferred partially or completely to the other hemisphere."

We are inclined to believe that better learning and reading occur when the controlling eye in binocular vision and the handedness result in the use of the original dominant hemisphere. If tests were ever devised that could locate this hemisphere in the newborn (but what about the 50% with no preference?) and the child's development could correspond without accident to this pattern, we could possibly eliminate this type of learning difficulty. As it now stands, the development of control with binocular vision on the same side as hand use gives an adequate result and relieves many children and adults of disabling difficulties in visual-motor coordination.

A comment on the reading from left to right had been included in our original material. This work was done at the University of Washington, about 1938. As you suspect, a left-handed, left-eyed person learns to read Hebrew more easily. We do not know of any reference to this kind of difficulty in learning to read vertically. However, we see vertical reversals, and *u* for *n*. They occur more frequently in children whose reversals are caused by hyperopia than in those whose reversals result from crossed control. Among the cultures who read vertically, education is so strictly limited to those who learn easily that the nature of a "learning difficulty" is probably not diagnosed. Those with difficulties are automatically eliminated.

Our problem is to educate all whose intelligence indicates that they can learn, and to do so regardless of what parents and/or culture has done to their hand use by school age. We believe that we have found an easily used and widely applicable solution to a condition which blocks learning in many otherwise normal children.

GEORGE E. BERNER, M.D.
5430 Greene St.
Philadelphia 44.

News and Comment

GENERAL NEWS

Joint Meeting of Section on Ophthalmology, American Medical Association, with Association for Research in Ophthalmology

TUESDAY AFTERNOON, JUNE 22, 1954

Chairman's Address — Trygve Gundersen, Boston

Choroidopathy — Arthur J. Bedell, Albany, N. Y.

Divergence Insufficiency — Donald J. Lyle, Cincinnati

Ocular Penetration of Procaine Following Subconjunctival Injection
Henry E. Schlegel and Kenneth C. Swan, Portland, Ore.

The Electroretinogram in Nyctalopia
John C. Armington and Gerald J. Schwab, Washington, D. C.

Elevated Lesions of the Macular Area: A Histopathological Study
William C. Frayer, Philadelphia

Use of Radioactive Phosphorus (P^{32}) in Differentiating Neoplastic from Other Intraocular Lesions
I. J. Eisenberg, I. S. Terner, and Irving H. Leopold, Philadelphia

WEDNESDAY AFTERNOON, JUNE 23

Executive Session

An Evaluation of Ocular Signs and Symptoms in Verified Brain Tumor
James F. O'Rourke and Nathan S. Schlezinger, Philadelphia

Some Aspects of Preparation, Sterilization, and Preservation of Ophthalmic Medications
John T. Murphy, Henry F. Allen, and Anita B. Mangiaracine, Boston

Adult Ocular Toxoplasmosis: A Preliminary Report of a Parasitologically Proved Case
Leon Jacobs, Bethesda, Md.; John R. Fair, and John H. Bickerton, Washington, D. C.

Periodic Unilateral Exophthalmos: Report of a Case
James E. Bennett, Cleveland

Heredomacular Degeneration — Corley B. McFarland, South Bend, Ind.

THURSDAY AFTERNOON, JUNE 24

Unilateral Blindness Occurring During Anesthesia for Neurosurgical Operations
Robert W. Hollenhorst, Hendrik J. Svien, and Clair F. Benoit, Rochester, Minn.

Beta Radiation Cataracts
James E. McDonald, William F. Hughes Jr., and Vincent G. Peiffer, Chicago

The Surgical Management of Nonparalytic Exotropia
ROBERT D. MULBERGER and P. ROBB MCDONALD, Philadelphia

Visual Changes in Malignant Exophthalmos JOSEPH IGERSHEIMER, Boston

Lymphomatous Tumors: A Clinical Follow-Up JOHN S. MCGAVIC, Bryn Mawr, Pa.

Lipochondrodysplasia (Gargoylism)
FRANK W. NEWELL and DOUGLAS N. BUCHANAN, Chicago, and AUNE KOISTINEN, Helsinki, Finland

Association for Research in Ophthalmology

WEDNESDAY, JUNE 23

Heterozygous Actions of Color-Blindness Genes GORDON L. WALLS

Participation of Different Groups of Cones in Human Dark Adaptation
EDGAR AUERBACH, M.D., and GEORGE WALD, PH.D.

Photography of the Anterior Segment of the Rabbit Eye
WILLIAM STONE JR., M.D., and LEONARD REYNOLDS

Effect of Alcohol on Binocular Vision
G. A. BRECHER, M.D.; A. P. HARTMAN, and D. D. LEONARD

An Experimental Study of Electroretinography: I. Electroretinogram in Experimental Animals Under the Influence of Methanol and Its Oxidation Products
J. PRAGLIN, PH.D.; R. SPURNEY, and A. M. POTTS, M.D.

Studies on the Visual Toxicity of Methanol: V. Role of Acidosis in Experimental Methanol Poisoning
A. P. GILGER, M.D., and A. M. POTTS, M.D.

Studies on the Visual Toxicity of Methanol: VI. Clinical Picture of Methanol Poisoning in Monkeys Treated with Base
A. M. POTTS, M.D.

The Liebmann Effect in Binocular Perception T. F. SCHLAEGEL JR., M.D.

THURSDAY, JUNE 24

Studies on the Anaerobic Metabolism of the Lens Capsule of Beef
ZACHARIAS DISCHE, M.D., and GABRIELLE EHRLICH, PH.D.

Anaerobic Carbohydrate Metabolism by Lens Extract
HARRY GREEN, PH.D., and CAROL A. BOCHER, M.S.

An Experimental Evaluation of Intraocular Streptokinase
JAMES O'ROURKE, M.D., and IRVING H. LEOPOLD, M.D.

Cytology of External Ocular Disease
S. J. KIMURA, M.D., and PHILLIPS THYGESON, M.D.

Further Studies on the Nature of the Exophthalmos Producing Principles in Pituitary Extracts
GEORGE K. SMELSER, M.D., and V. OZANICS

Changes in the Organic Phosphate Fractions of the Lens JOHN E. HARRIS, M.D.

Transport of Glucose Across the Lens Capsule JOHN E. HARRIS, M.D.

Nonstriated Muscle of the Human Orbit WALTER H. FINK, M.D.

FRIDAY, JUNE 25

Effects of Carbonic Anhydrase Inhibition of the Eye BERNARD BECKER, M.D.

Study of the Growth of the Anterior Corneal Layer in Relation to the Plastic Artificial Cornea WILLIAM STONE JR., M.D.

An Unsuccessful Attempt to Produce Hypersensitivity to Uveal Tissue in Guinea Pigs HOWARD A. NAQUIN, M.D.

Electrophoretic Studies of Tears W. K. MCEWEN, PH.D., and S. J. KIMURA, M.D.

Panuveitis in Hamsters with Chronic Toxoplasma and Besnoitia Infection J. K. FRENKEL, M.D.

Studies of Immunity in Experimental Herpetic Keratitis in Rabbits RAY L. HALL, M.D.; RUTH G. MACKNEESON, B.A., and H. L. ORMSBY, M.D.

Intraocular Penetration of Magnamycin HANS HAUSSLER, M.D., and H. L. ORMSBY, M.D.

Effect of Various Media on the Growth of Corneal Epithelium in Tissue Culture MRS. ANNE FOWLE, PH.D., and H. L. ORMSBY, M.D.

Abstracts will appear in the program issue of *The Journal of the American Medical Association.*

Pan-American Congress of Ophthalmology.—The Pan-American Association of Ophthalmology will hold its Third Interim Congress June 17 to 21 in São Paulo, Brazil, under the presidency of Dr. Moacyr E. Alvaro, of São Paulo. The meeting is of special interest because it is one of many official events in the celebration of the quadricentennial of the host city this year.

The scientific program includes papers by several physicians of the United States, as follows:

Intraocular and Orbital Tumors.....Dr. Ray K. Daily, Houston, Texas
Acute Inflammatory Glaucoma.....Dr. H. Saul Sugar, Detroit
Diseases of the Retina.....Dr. W. Banks Anderson, Durham, N. C.
Diseases of the Optic Nerve.....Dr. Curtis Benton Jr., Fort Lauderdale, Fla., with Dr. Jorge Valdeavellano, Lima, Peru
Medical Treatment of Strabismus.....Dr. Murray McCaslin, Pittsburgh
Surgery of Retinal Detachment.....Dr. Charles L. Schepens, Boston

Papers by ophthalmologists of the other countries of the hemisphere include the following:

Simple Chronic Glaucoma.....Dr. Santiago Barrenechea, Santiago, Chile
Correction of Ametropias.....Dr. Baudilio Courtis, Buenos Aires, Argentina
Lids and Lacrimal Apparatus.....Dr. Washington Isola, Montevideo, Uruguay
The Orbit.....Dr. Humberto Escapini, San Salvador, El Salvador
Uveitis.....Dr. Henri Pichette, Quebec, Canada
Plastic Operations on the Lids.....Dr. Rebelo Neto, São Paulo, Brazil
Surgical Treatment of Concomitant and Paralytic Strabismus..Drs. José Angel Ramirez and Luis E. Mendez, Carácas, Venezuela

Presentations will be in English, Spanish, or Portuguese, with simultaneous translations into the other two languages.

There will be a registration fee of $10, which will cover many special events, as well as attendance at two other congresses which will be meeting at the same time. These are the Eighth Brazilian Congress of Ophthalmology and the Nineteenth International Congress of Oto-Neuro-Ophthalmology. Attendance is not limited to members of the Pan-American Association of Ophthalmology, Dr. Alvaro has announced.

Many social events have been planned by Brazilian ophthalmologists, including opportunities to become acquainted with typical Brazilian activities, such as coffee growing. A large exposition is a feature of the quadricentennial celebration of São Paulo.

The Pan-American Association of Ophthalmology was founded in 1939 by a committee consisting of the late Dr. Harry S. Gradle, Chicago, who was its first president; Dr. Conrad Berens, New York, the second president, and Dr. Alvaro, the present president. Congresses were held in Cleveland in 1940; in Montevideo, Uruguay, in 1945; in Habana, Cuba, in 1949, and in México, D. F., Mexico, in 1952. The First Interim Congress met in Miami Beach, Fla., in 1950, and the second on a Caribbean cruise in 1953.

Course on Glaucoma.—A course on glaucoma, with particular emphasis on gonioscopy and study of the anterior angle, will be given at the Brooklyn Eye and Ear Hospital on May 17, 18, and 19, 1954. Ample opportunity for practical instruction in the use of the goniolens will be given, and material from the glaucoma clinic will be utilized. The course will be given by Dr. Daniel Kravitz, assisted by Dr. Walter V. Moore, Dr. Mortimer A. Lasky, Dr. Harold F. Schilback, and Dr. Arthur Shainhouse. Registration is limited to six ophthalmologists only.

Application and the fee of $40 may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38.

Dedication of Proctor Foundation Laboratories.—The Department of Ophthalmology of the University of California School of Medicine at San Francisco announces the dedication on Sept. 29, Sept. 30, and Oct. 1 of the new laboratories of the Francis I. Proctor Foundation for Research in Ophthalmology, which was established in 1946 by Mrs. Proctor in memory of her husband.

These laboratories, whose construction was made possible through the generosity of Mr. and Mrs. Berthold Guggenhime, occupy an area of 3,000 sq. ft. in the new Medical Sciences Building, which is nearing completion. They will provide facilities for ophthalmological research in microbiology, pathology, physiological chemistry, and physiological optics. Other research activities of the Foundation will be conducted in the E. S. Heller Laboratories, which were donated in 1941 for research in ophthalmology and have been temporarily occupied by the Proctor Foundation, pending the completion of the new building.

On Wednesday afternoon, Sept. 29, the staff of the Department of Ophthalmology and of the Proctor Foundation will hold open house at the new laboratories, and on Thursday and Friday a two-day scientific program will be presented at the Morrison Auditorium in Golden Gate Park. The guest speakers will include Sir Stewart Duke-Elder, London, England; A. Franceschetti, Geneva, Switzerland; Giambattista Bietti, Parma, Italy; Josef Bock, Graz, Austria; Norman Ashton, London, England; M. Puig Solanes, México D. F., Mexico; Hugh L. Ormsby, Toronto, Canada; Frederick H. Verhoeff and David G. Cogan, Boston; Alan C. Woods and Jonas S. Friedenwald, Baltimore; Algernon B. Reese, New York; Derrick Vail, Peter C. Kronfeld, and Georgiana D. Theobald, Chicago; Kenneth C. Swan, Portland, Ore.; Colonel John H. King Jr., Washington, D. C., and S. Rodman Irvine, Beverly Hills, Calif. On Thursday evening Dr. Ludwig von Sallmann will deliver the ninth Francis I. Proctor Lecture.

Eyes for Uveitis Laboratory, University of California Medical Center.—The Uveitis Laboratory, Medical Research, Department of Ophthalmology, University of California Medical Center, San Francisco 22, urgently requests all physicians to send freshly enucleated eyes from cases of diffuse uveitis, irridocyclitis, and chorioretinitis for cultural and pathological studies. The eyes should be placed in a sterile bottle, *not* fixed in formalin, and sent as quickly as possible, air express collect, to Dr. Michael J. Hogan, Director, Francis I. Proctor Foundation for Research in Ophthalmology. A complete report will be sent on each specimen received.

The laboratory would also like to obtain formalin-fixed specimens of similar eyes for pathological study.

Books

The Book of Health. By R. Lee Clark Jr., M.D., and Russell W. Cumley, Ph.D., Editors. Price, $12.50. Pp. 836, with 1,500 illustrations (20 color plates). Elsevier Press, Inc., 155 E. 82nd St., New York 28, 1953.

This is an excellent book for the layman and answers most of his questions about illness in a concise and clear manner. The chapter on the eyes is well done. The only criticism which could be made is the emphasis which is placed on keratoplasty, to the extent of including pictures of the operative procedure. Although undoubtedly of great interest to the public, much useful information regarding eye care must have been eliminated in order to make room for this.

The Basis of Clinical Neurology. By Samuel Brock, M.D. Price, $7.00. Pp. 510, with 124 illustrations. William & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1953.

The third edition of this well-known text contains many revisions which keep the book up to date. The section on the visual pathways has been revised by Dr. Max Chamlin, who also has contributed to the section on ocular movements. As in the previous edition, the approach to the subject matter is physiological, and there is much of value for the ophthalmologist throughout the book.

Medical Progress. Edited by Morris Fishbein. Price, $5.00. Pp. 332. The Blakiston Company, Inc., 575 Madison Ave., New York 22, 1954.

The various fields of medicine and surgery are covered concisely by an impressive group of subeditors. Since the whole book is only 332 pages, the keynote has been condensation. Ophthalmology has been well reviewed by Manuel L. Stillerman, who has laid special emphasis on retrolental fibroplasia; the use of cortisone, hydrocortisone, and corticotropin; intraocular acrylic lenses, and preventive ophthalmology.

The book is presumably for the use of the general physician, and the only criticism that can be raised is how useful a book of this kind is to a reader with limited knowledge in all the fields treated.

Affections vasculaires de la rétine. By P. Bailliart. Price, 3,200 francs. Pp. 407, with 111 illustrations (4 color plates). Gaston Doin & Cie, 8 Place de l'Odéon, Paris 6e, 1953.

Bailliart was one of the pioneers in measuring the retinal arterial pressure with the dynamometer, and although the method is not used routinely in this country, it has considerably advanced our knowledge of the hemodynamics of the eye in many ocular diseases and in those conditions in which the arterial and venous pressures in the cerebral circulation undergo pathologic changes. This monograph, in French, covers all the vascular affections of the retina, with special emphasis on the knowledge which has been gained by this method. The first eight chapters deal with the anatomy, embryology, and physiology of the retinal circulation. The rest of the book documents the changes occurring in the retina and the diseases which are primarily of vascular origin or express themselves in changes in the retinal circulation. The bibliography is particularly extensive throughout the text; in fact, one criticism which can be made of this and so many other books is the discontinuity created in piecing together the literature, so that the whole text reads like a compilation of

individual papers. This has its value for those who are searching the literature for individual references but does break up the continuity of thought. The illustrations are excellent.

Elektrochirurgie am Auge (Electrosurgery on the Eye). By Karl Safar. Price, $8.60. Pp. 178, with 56 text illustrations (116 separate pictures), part in color. Springer-Verlag, Mölkerbasrei 5, Wien 1, 1953.

This text, in German, describes the various uses of electrosurgery in diseases of the eye. A short introduction covers the principles involved with the use of galvanocautery, electrolysis, and diathermy. The rest of the book describes diseases of the various parts of the eye in which electrosurgery has been found useful by the author, beginning with the lids and ending with detachment of the retina.

For those who read German this book will be found of real practical value. Preoperative and postoperative treatment and complications are dealt with in a concise and clear manner, and the illustrations are excellent. Many are in color. An excellent bibliography is appended.

Current Therapy—1954. Howard F. Conn, M.D., Editor. Price, $11. Pp. 898. W. B. Saunders Company, W. Washington Sq., Philadelphia 5, 1954.

This is the sixth of the annual series which have brought to the busy physician current methods of treatment in a concise and easily found form. While there is not a great deal which relates to ophthalmology in any of these excellent books, they are well worth having in any library.

This volume brings current therapy up to date.

Objektive Prufung der Sehleistungen mit Hilfe der optokinetischen Augenbewegungen. By Prof. Dr. med. Johannes Ohm. Price, not given. Pp. 181, with 135 illustrations. Ferdinand Enke, Hasenbergsteige 3, Stuttgart, Germany, 1953.

This small monograph considers the general significance of optokinetic nystagmus in all its phases. The author is well known for his writings on nystagmus during the past twenty-five years. This study deals with the estimation of visual acuity by means of optokinetic nystagmus, and in particular the effect of various disease processes on the optokinetic pendulum type of nystagmus. It will be useful only for those who are particularly interested in using this phenomenon for experimental purposes.

PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc.*

O

C U

L A R

I N F E C

T I O N S

R E S P O N D

T O B R O A D

S P E C T R U M

T E R R A M Y C I N®

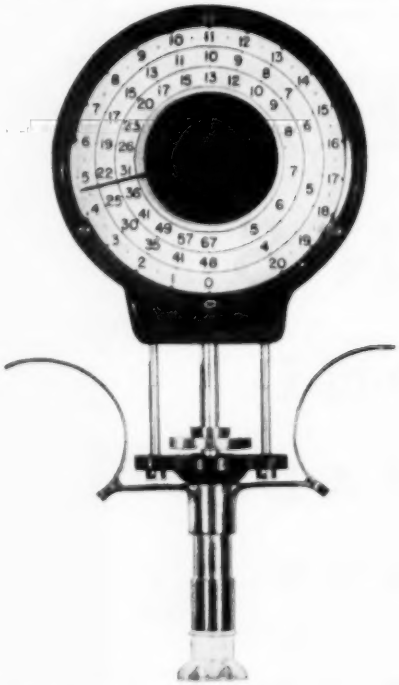
BRAND OF OXYTETRACYCLINE

OPHTHALMIC INSTRUMENTS
OF PRECISION

Theodore Hamblin Ltd

GUILD OPTICIANS

15 WIGMORE STREET,
LONDON, W.1.
ENGLAND.



The New

HARRINGTON TONOMETER

This is an extremely accurate instrument.

The dial has three scales, the outer being the expanded Schiotz scale, 0 to 20, the middle and inner scales being direct readings in millimeters of mercury for the 5.5 and 7.5 gram weights.

10 and 15 gram weights are included. with conversion table.

Descriptive leaflet sent on request.

Fully guaranteed

PARSONS OPTICAL LABORATORIES

518 Powell Street San Francisco 2, Calif.

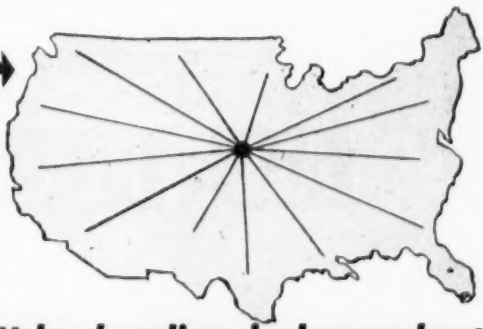
BROADWAY *to* MAIN

BIG *or* SMALL
We Serve them all!

From Memphis to Mobile, from Broadway at 42nd to Hollywood and Vine, we supply Ophthalmologists with all optical requirements. From the smallest community to the largest metropolitan city, doctors throughout the United States, Mexico, and Canada have learned, through the past 25 years, that Commercial Optical of Omaha can be depended upon to supply a wide variety of frames, lenses of any description, and other optical supplies. Our competitive prices assure you of extra benefits for your patients, and our centrally located plants in Omaha and Kansas City assure you of prompt Air Mail and Regular Mail service.

OVER-NIGHT AIRMAIL SERVICE
anywhere in the U.S.A., Mexico, or Canada

We feature quality merchandise from nationally known manufacturers such as Titmus, Universal, Artcraft, Victory, Continental, and Optical Products Company.



"the leading independent Rx laboratory in the U.S."

Quality Rx Service at substantial savings for your patients

Commercial OPTICAL COMPANY
Wholesale Optical Supplies

321 SOUTH 15TH STREET ... OMAHA 2, NEBR.
or Box 2177 Kansas City, Missouri

Clip and Mail the Coupon today

AMA-4

COMMERCIAL OPTICAL CO.
321 SO. 15TH ST., OMAHA, NEBRASKA
Or — Box 2177 — Kansas City, Missouri

- ☐ Send 1954 DIVIDEND OFFER
- ☐ Send 1954 Fashion Catalog
- ☐ Send your latest price list, prepaid airmail envelopes, Rx book, and supplies.
- ☐ Send monthly bulletin of specials

NAME _____

STREET _____

CITY _____ STATE _____

Rx

QUALITY SERVICE

Technical skills and services that will never let you down

DOW

CONFIDENCE...

Professional reputations are built on confidence. Your learning and skill and judgment would be fruitless unless you strove to achieve faith on the part of your patients. And even when you have won this trust all your effort is at the mercy of those who interpret your prescriptions.

¶Here at Dow we pride ourselves on the impeccable quality of our eye-wear, which results inevitably from our scrupulous selection of only top-grade materials . . . from the care with which we grind and polish and edge our lenses . . . from our expert placement of them before the eyes in the very best of mountings. All this and more we do . . . that your patients may have fullest confidence in you.

DOW OPTICAL CO.

W. E. DOW, Pres.

Chicago, Ill. Bloomington, Ill.

ALL PLASTIC

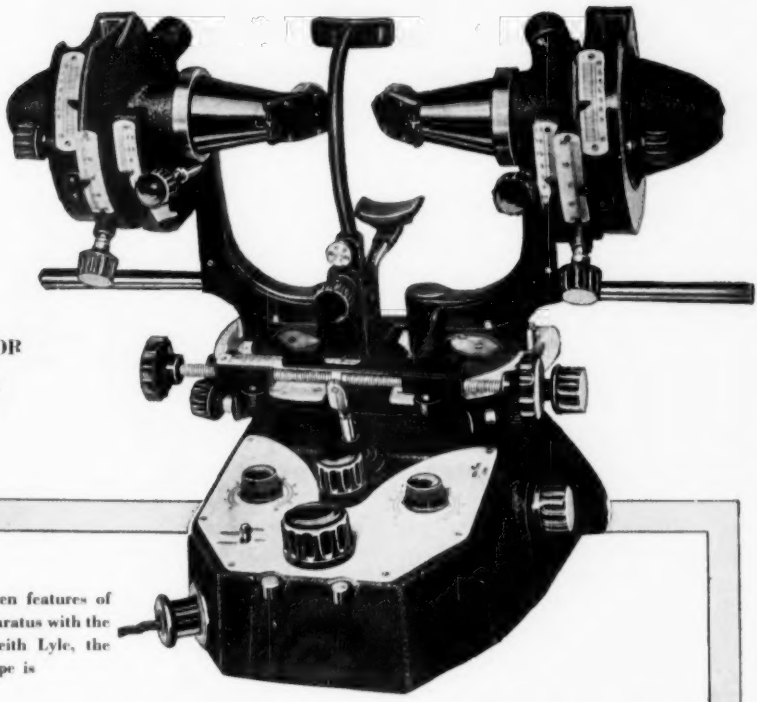
ARTIFICIAL EYES

Individually Created

DAVID A. GROSSBERG INC.

133 EAST 58th STREET NEW YORK 22, N. Y

WICKERSHAM MEDICAL BLDG.



THE LYLE MAJOR AMBLYOSCOPE

(Standard Model)

Incorporating the proven features of previous Synotype apparatus with the suggestions of Mr. Keith Lyle, the Lyle Major Amblyoscope is

The Most Advanced British Orthoptic Apparatus Produced

Specially manufactured to meet the demands of present day technique, the Lyle Major Amblyoscope, Standard Model, incorporates the following improved features :

1. Elevation and Depression Device
2. Increased range of Duction Control
3. Non-slip Duction Locks
4. Increased Hyperphoria Movement
5. Transparent breath shield
6. Hinged Mirrors and Reflectors
7. Noiseless Slide Carriers
8. Supported main roller bearings and increased mechanical strength
9. Large, easily visible scales
10. Concealed wiring
11. Separate electrical circuits to each optical tube
12. Improved hand flashing switches
13. Provision for automatic moving picture attachment

Specialists in Orthoptic Equipment including :

MOORFIELD'S SYNOPTOPHORE · HESS SCREENS · CHEIROSCOPES · WORTH'S 4 DOT TEST · DIPLOPIA GOGGLES · ROTATING E TEST · MADDOX HANDFRAME · MADDOX WING TEST BAR READERS · ETC.

CLEMENT CLARKE

of England · **63, WIGMORE STREET, LONDON, W.1**

E. B. Meyrowitz

SURGICAL INSTRUMENTS CO., INC.,
520 FIFTH AVENUE, NEW YORK 36, N. Y.

LONDON — *ESTABLISHED 1875* — PARIS

Now Available Again

BRAUN'S TONSILLOTOME

Combination of Sluder and Two Snares

It minimizes hemorrhage and shock, diminishes the amount of trauma, shortens the time required for the enucleation, and obviates the complications that often ensue.

Price Complete $72.50

WOLF COMBINATION MOUTHGAG AND TONGUE DEPRESSOR

This consists of a mouthgag without interfering or projecting parts and a tongue depressor which can be used with or independently from the mouthgag.

Price, $17.50

New developments in facial restoration

Undoubtedly, reconstructive surgery is the ideal treatment for congenital defects and loss of a facial organ or symmetry either by accident, disease or surgical extirpation. There are numerous instances where it is preferable to replace a removed or distorted structure with an artificial appliance.

Patients who either lose or have a distorted feature of the face represent a serious problem in vocational and psychosocial readjustment.

After the fitting of a facial appliance, case histories show that the majority of patients are restored to a position of self-respect and economic self-sufficiency.

Write For Free Pamphlet

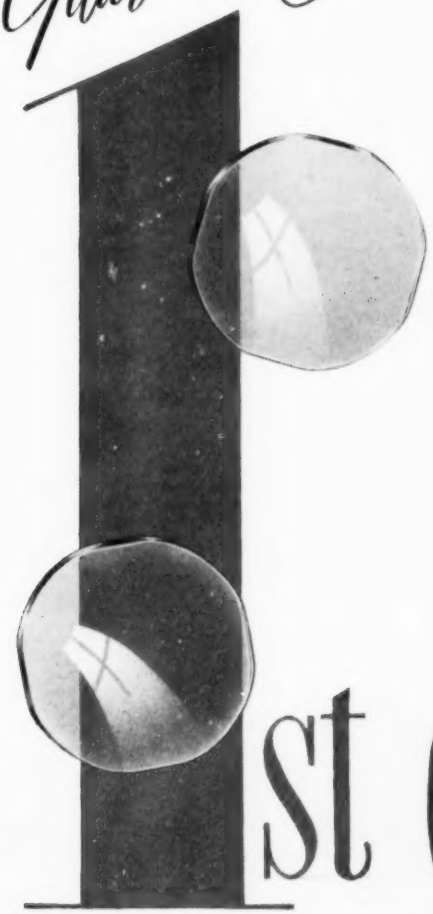
Serving the Profession Since 1851

Mager and Gougelman, inc.

30 NORTH MICHIGAN AVENUE • CHICAGO 2, ILLINOIS

DETROIT • CLEVELAND • KANSAS CITY • MINNEAPOLIS • NEW ORLEANS • ST. LOUIS
NEW YORK • BOSTON • BUFFALO • PHILADELPHIA • PITTSBURGH • WASHINGTON

Guaranteed



1st quality

WIDESITE
CORRECTED CURVE LENSES
WHITE AND TONETEX

Shuron's Widesite Corrected Curve Lenses, through marginal astigmatic correction, offer greater visual comfort and efficiency for your patient. The corrected curve permits clear vision from center to edge of lens. The patient's eyes see as nature intended them to see.

Widesite lenses are of the finest quality obtainable. Finish is free from aberrations, with fine surface polish. Free from bubbles, seeds and striae. Centering and powering are correct. Thickness is accurately controlled.

SHURON OPTICAL COMPANY, INC.
GENEVA, N. Y.

T354-2

Specify SHURON for First Quality

Better-Surer-Safer Than Ever

THE MUELLER GIANT EYE MAGNET

An Improved Model
With Spark-Free, Noiseless Selenium Rectifier
Explosion-Proof Footswitch Control

Particularly where industrial injuries are frequent, the improved Mueller Giant Eye Magnet is essential equipment for the modern hospital, clinic, first aid room. The most powerful magnet of its type ever built, it is so flexible, so easily controlled, that it is actually a precise instrument capable of the most delicate maneuvering. It is adjustable in tilt, direction and height, perfectly counterbalanced, tip-proof, will not slip from any set position. It is shockproof to both patient and operator. Equipped with rheostat power control, sterilizable probe tip. Requires no special connections. Rolls on noiseless casters. *And it is not expensive.*

TWO MODELS AVAILABLE

The Giant Magnet is built with selenium rectifier, for use on 115 volts, AC; and without the rectifier, for use on 115 volts, DC. Write for prices and delivery information.

Instrument Makers To The Profession Since 1895

V. Mueller & Co.

330 SOUTH HONORE STREET
CHICAGO 12, ILLINOIS

Night Driving Demands

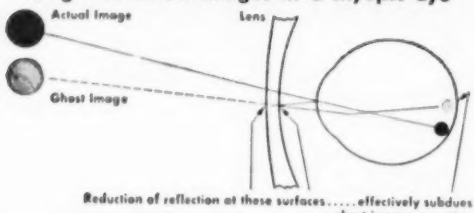
Lestra-Lite
Reg. U.S. Pat. Off.

OPHTHALMIC LENS COATING

"There IS a Difference"

Reflections from eye-glass surfaces are most distracting while driving at night. Light reflected between the front and back lens surfaces and between the cornea and lens surfaces intensifies the glare of oncoming headlights, reducing the driver's visual discrimination. For easier, safer night driving, *always* prescribe Lestra-Lite.

Origin of Ghost Images in a Myopic Eye



Reduction of reflection at these surfaces.....effectively subdues ghost images on retina

FAST LESTRA-LITE SERVICE { Lenses processed and returned postpaid same day as received.

Write for half-coated Lestra-Lite Sample and Literature.

PACIFIC UNIVERSAL PRODUCTS CORPORATION
158 Vista Avenue • Pasadena 8, Calif.
130 Bush Street • San Francisco 4, California

POSTGRADUATE COURSE
and
SUMMER CONVENTION OF THE COLORADO OPHTHALMOLOGICAL SOCIETY
at the
UNIVERSITY OF COLORADO MEDICAL CENTER
Denver, Colorado
July 26, 27, 28, 29, 1954

The program will consist of lectures, seminars and demonstrations of interest to both the specialist and the practitioner caring for Eye Diseases.

Registration will be open to all members of the Society and qualified physicians on a limited membership basis. Tuition $40.00.

Plan now to attend and combine an intensive review of advances in this specialty with your summer vacation.

Complete program and details will be mailed upon request addressed to:

Director of Graduate and Postgraduate Medical Education
University of Colorado School of Medicine
4200 East Ninth Avenue
Denver 20, Colorado

And now ... The MODERN

JUMBO 3-Way

... for the smooth transition of continuous, uninterrupted vision ...

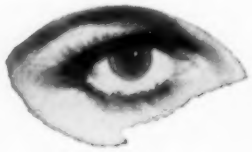
by MODERN OPTICS *Incorporated*

HOUSTON, TEXAS

Four MODERN 3-Way Segs:–

JUMBO · Flat Top · 8mm Flat Top · Round Top

"Must be MODERN!"



Most Natural
ARTIFICIAL EYES

Dispensers and makers of fine eyes of plastic and glass. Eyes to fit all types of implants.

Selections sent on memorandum from the most complete group of eyes. Careful attention given to all referred cases.

The Doctor and his patient must be completely satisfied or there is absolutely no obligation.

Of Service Since 1906

DENVER OPTIC COMPANY

310 University Bldg. Telephone Main 5638 Denver 2, Colorado

The Berman Metal Locator

An electromagnetic detecting device that quickly and accurately locates metallic foreign bodies, including magnetic intraocular foreign bodies. Metallic fragments are readily detected from a satisfactory distance through intervening bone, tissue and fluids. Probing or physical contact with the foreign body is not required for detection.

The thin sterilizable probe provides preoperative localization, "pin-point" accuracy within the incision and postoperative check.

Lends precision to foreign body surgery and greatly reduces surgical trauma.

BERMAN LABORATORIES
534 West 42nd Street New York 18, N. Y.

I Hide Your Eyes

Says Gary Ghost

When a person has his picture taken wearing glasses, ever notice the reflections on the lenses? These are "ghost images." MAY-O-LITE, a Low Reflection Lens Coating, reduces reflections up to as much as 95 per cent, yet increases light transmission.

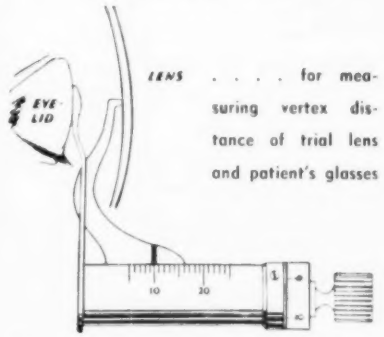
Complete Your Professional Service By Adding

The Best in Sight
MAY-O-LITE
Low Reflection Coating

MAY RESEARCH, INC., Box 1181, Minneapolis 1, Minn.

For Trial Frame
The Lenscorometer

originated by Austin Belgard

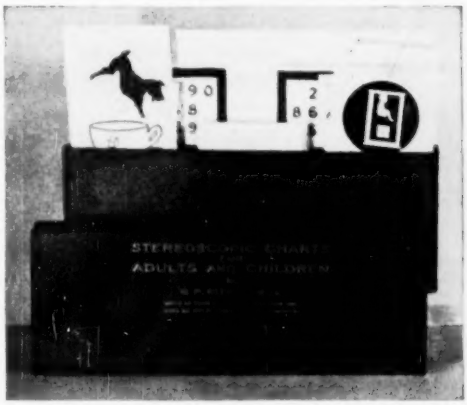


Use of Lenscorometer in all cases of aphakia, + OR — corrections of four diopters or more—a necessity to insure true translation of prescription.

Each $11.75

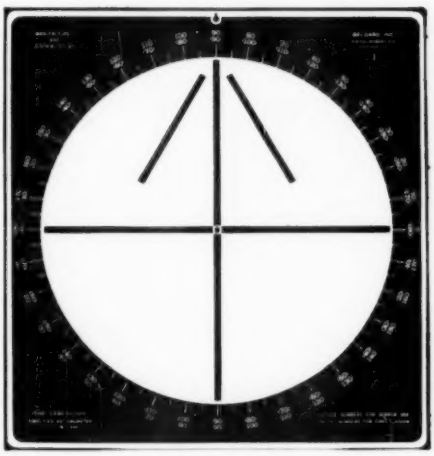
Stereoscopic Cards

by GUIBOR



Can be used with the Stereocampimeter, Synoptoscope, Rotoscope and similar instruments; also with regular stereoscope. For adults and children.

Set $4.75



(Actual size 13½" x 14")

SIMPLIFIED ASTIGMOMETER

(Lebensohn)

PLASTIC

WASHABLE

"NO COMPUTATION REQUIRED"

CAN BE USED AT 10 OR 20 FEET

Send for Literature

EACH $9.75

Austin Belgard INC.

(Formerly Belgard, Inc.)

OPHTHALMIC OPTICIANS

WHOLESALE & SERVICE

DISPENSING SERVICE

109 N. Wabash, at Washington
9th Floor STate 2-5362
CHICAGO, ILL.

Medical Center Office:
1920 W. Harrison St., at Ogden
CHICAGO, ILL.

All of the following articles have appeared in TODAY'S HEALTH and are now available in pamphlet form.

ALCOHOLISM

an important problem in today's living

ALCOHOLICS ANONYMOUS

Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.
4 pages, 10 cents

ALCOHOL AND CIRRHOSIS OF THE LIVER

Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences.
by Russell S. Boles
4 pages, 10 cents

HOW TO HELP A PROBLEM DRINKER

Understanding the alcoholic's capabilities, the necessity of help, causes of his condition.
by Edward A. Strecker and Francis T. Chambers, Jr.
4 pages, 10 cents

THE TREATMENT OF ALCOHOLISM

Tracing the steps from convincing the alcoholic that he is sick through treatment and cure.
by Lewis Inman Sharp
4 pages, 10 cents

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM

Its place among methods of treatment today, its development and correlation with personality factors.
by Walter L. Voegtlin
4 pages, 10 cents

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM

Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel.
by E. H. L. Corwin
4 pages, 10 cents

THE ABOVE SIX PAMPHLETS ARE ALSO AVAILABLE IN BOOKLET FORM FOR ONLY 50 CENTS

HOW TO MEASURE DRUNKENNESS

A partial transcript of an actual courtroom case.
H. A. Heise
8 pages, 10 cents

ADDRESS REQUESTS TO:

BUREAU OF HEALTH EDUCATION
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

New!

the most talked about

FAME
ASTRAL
EXECUSPEC

frames of the year

Kono's unique marriage of zyl and metal —the "made for each other" modern design . . . the newest, most fashionable frame-look for men and women! The slim, lightweight METAKON temple is a Konoptic creation in eyeline beauty!

FAME
Austrian crystals gem—set on fronts and temples.

ASTRAL
. . . costume colored plastic made more enchanting with slim metal temples and astral trim.

EXECUSPEC
A new frame style for men!—smart metal temples and crisp tailored trim.

© KMC

THE KONO MANUFACTURING COMPANY
69-24 FORTY-NINTH AVE., WOODSIDE, N. Y.
Los Angeles, Calif. • Chicago 11 • Atlanta, Ga. • Charleston, S. C. • Columbus, O.

AVAILABLE THROUGH YOUR KONOPTIC SUPPLY HOUSE

NOW– MORE ACCURATE VISUAL DIAGNOSIS IN THE EYE, EAR, NOSE AND THROAT

WITH THE NEW, IMPROVED

A.C.M.I. DIAGNOSTIC SETS

American Cystoscope Makers offers the medical profession the finest line of Diagnostic Sets in its entire history. These new sets incorporate the outstandingly important feature —exclusive with the ACMI ophthalmoscope—of a coated lens system, greatly increasing the amount of light transmitted, improving definition and clarity of the image, and eliminating halo, flare and ghost images.

STANDARD SET comprises ophthalmoscope head (with built-in color filter and aperture changer), otoscope head with 3 specula, medium battery handle and one spare lamp, in plush-lined case, with space for additional specula and tongue depressor.

COMPACT SET, for the practicing physician, includes ophthalmoscope head (with built-in color filter and aperture changer), otoscope head, 5 ear and 1 nasal specula, small battery handle and extra lamp. Additional space for tongue depressor and more specula.

LARGE SET contains otoscope head, 5 ear and 1 nasal specula, ophthalmoscope head (with built-in color filter and aperture changer), large battery handle, 1 extra lamp, with provision in case for tongue depressor head, additional specula and lamp replacement.

PROFESSIONAL SET. This, the most complete Wappler set, incorporates an otoscope head with 5 ear and 1 nasal specula, tongue depressor head, ophthalmoscope head (with built-in color filter and aperture changer), large battery handle, extra lamp, and rubber bulb for insufflation.

Standard Set, Catalog No. 1106

Compact Set, Catalog No. 1107

Large Set, Catalog No. 1109

Professional Set, Catalog No. 1111

AMERICAN CYSTOSCOPE MAKERS, INC.

Frederick J. Wallace, President

1241 LAFAYETTE AVENUE • NEW YORK 59, N. Y.

ALL SPARKLE AND GLITTER –

Royal Baguette

The New Trim for ART-RIM Leading Lady Frames

Long cut imported Austrian baguettes with round-cut rhinestone in a 1/10-12K Pink or White Gold Filled setting.

MANUFACTURER • **ART-CRAFT OPTICAL CO. INC.** 89 ALLEN STREET ROCHESTER 6, N. Y.

• *DISTRIBUTED BY* •

ART CRAFT OPTICAL OF NEW YORK CITY, INC.
ART CRAFT OPTICAL OF PHILADELPHIA, INC.
ART CRAFT OPTICAL OF CHICAGO, INC.
ART CRAFT OPTICAL OF NEW ENGLAND, INC.
ART CRAFT OPTICAL—MIDWEST, INC.
ART CRAFT OPTICAL—SOUTHEAST, INC.
ART CRAFT OPTICAL—WEST COAST, INC.
ART CRAFT OPTICAL OF THE SOUTH, INC.
ART CRAFT OPTICAL—NORTH CENTRAL, INC.
ART CRAFT OPTICAL OF ROCHESTER, INC.
ART CRAFT OPTICAL—MIDDLE ATLANTIC, INC.
ART CRAFT OPTICAL—SOUTHWEST, INC.
ART CRAFT OPTICAL OF CANADA, LTD.
ART CRAFT OPTICAL—INTERAMERICANA, INC.
ART CRAFT OPTICAL EXPORT CORP.

BVI

The Hallmark of Fine Quality . . .

For over thirty years, Century Oxford's "C" has inspired confidence and faith throughout the profession. It represents perfection of design and precise execution of perfect frames.

Through the exclusive use of fine quality materials and modern machinery, Century Oxford *has earned and maintained* its distinguished reputation for producing frames unsurpassed in fashionable beauty, greater comfort and precision-perfect accuracy.

When you see the famous "C" of Century Oxford, be assured that you are looking at one of the country's finest frames . . . cosmetically and ophthalmically correct in every possible respect.

send for
NEW FREE
STYLE CATALOG

Century

Century Oxford Manufacturing Corp., 200 60th Street, Brooklyn 20, N. Y.

Branch office: Blymer Bldg., Cincinnati, Ohio.